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Autumn—1946
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ANNALS OF
INTERNAL MEDICINE

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THE PROBLEM OF PROLONGED HEPATITIS WITH PARTICULAR REFERENCE TO THE CHOLANGIOLITIC TYPE AND TO THE DEVELOPMENT OF CHOLANGIOLITIC CIRRHOSIS OF THE LIVER*

By CECIL JAMES WATSON, M.D., Ph.D., F.A.C.P., and FREDERICK WILLIAM HOFFBAUER, M.S., M.D., *Minneapolis, Minnesota*

BOTH sporadic and epidemic jaundice have been generally referred to for many years as "catarrhal" in character. It is well known that this term stems from the early concept of Bamberger [1] and Virchow [2] of a catarrhal or mucous inflammation of the papilla of Vater, a concept which appears to have been an elaboration, on the grounds of anatomic studies, of the so-called "gastroduodenal catarrh and jaundice" of the earlier Irish clinicians, notably Stokes [3] and Graves.[4] The earlier literature has been adequately reviewed by Eppinger [5] and Lichtman.[6] Attention may be called again to the clear statement of Flindt [7] in 1890, that so-called catarrhal jaundice is, in the main, a diffuse parenchymatous liver disease rather than a catarrh of the ampulla. A number of years later, during World War I, Eppinger [8] studied the livers of four soldiers killed in action, who were suffering from "catarrhal" jaundice at the time of death. In each instance the papilla of Vater and the bile ducts appeared normal, but the liver exhibited the histologic picture of an "acute destructive hepatitis." Entirely similar findings and conclusions were reported by Lindstedt,[9] later by Klemperer, Killian and Heyd,[10] and by Gaskell.[11] Recent studies [12, 13] of liver histology, as afforded by aspiration liver biopsy, have quite uniformly confirmed these earlier reports so that it may now be accepted that what has hitherto been designated as catarrhal

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jaundice is hepatitis, with but rare exception. Eppinger [5] emphasizes the great rarity of true catarrhal jaundice or papillitis by pointing out that but three cases have ever been proved at necropsy.

Past wars have had their epidemics of jaundice, the "jaundice of the camps," or "of the campaign." The disease was common in the American Civil War, in the Crimean War, and in the Balkan campaigns of World War I. In the present war epidemic hepatitis has been a medical problem of the first order of magnitude, often "second in importance only to malaria and venereal disease." [14] This is scarcely surprising when one considers the important factors contributed by three of the four horsemen, i.e. (1) war; the crowding, poor sanitation and fatigue incident to it, (2) famine; the deleterious effect of malnutrition on the liver, and (3) pestilence; the reduction of the resistance of the liver incident to other infections, notably those of the Salmonella and Shigella groups. The frequent association of hepatitis with the latter group of diseases is well known.

Unfortunately enough, the incidence of hepatitis in World War II has been considerably increased in the attempt to limit or prevent other diseases. The transmission of icterogenic agents to healthy individuals has occurred through the administration of pooled serum or plasma, or products containing one or the other, as for example yellow fever vaccine as formerly used.[15, 16, 17] This type of hepatitis has come to be known as "homologous serum jaundice," regardless of whether the source was yellow fever vaccine, measles or mumps convalescent serum, or whole blood or plasma transfusions. The subject of homologous serum jaundice has been thoroughly considered in several recent papers.[15, 18, 19, 20, 21] The incubation period of this type of hepatitis, usually in the neighborhood of 60 to 120 days, is usually more than twice as long as that of the spontaneous form.[21c] This difference has been regarded by many as indicating a different etiology, but it is entirely possible, as suggested by Neefe and his co-workers,[21a] that the length of incubation period is determined by the portal of entry. This is also indicated by the studies of Havens and his co-workers.[22a] Furthermore, the study of Neefe and his associates [21] revealed clearly that hepatic involvement following injection of icterogenic serum, is commonly present long before the appearance of jaundice, if carefully sought by means of suitable laboratory tests. Recent studies by Neefe and co-workers [21b, c] indicate strongly that the diseases are at least immunologically distinct. Siede and Luz [23] have reported serial passage of the virus of the epidemic type in chick embryos and interestingly enough, the livers were found to be most susceptible. These results have not been confirmed.

Witts [14] has postulated a fundamental difference between homologous serum jaundice and the spontaneous epidemic variety on the basis of an increased susceptibility to the latter in individuals having had the former. One might take the opposite viewpoint, however, that an immunity is not conferred, and that the liver is simply rendered more susceptible by the first

attack. Multiple attacks of sporadic or so-called "catarrhal" jaundice, in the same individual, are very well known, and have also been observed in the epidemic form.[23] Oliphant's studies[24] were of much interest to this whole question. These observations, although limited to a small series of volunteers, indicated that an attack of homologous serum jaundice 12 to 18 months previously, appeared to confer an immunity against subsequent infection whether of the spontaneous variety, or that due to yellow fever vaccine containing human serum. As indicated above, however, the more recent studies of Neefe and his associates,[21c] and of Havens [22b] failed to reveal cross immunity.

Regardless of whether the icterogenic agent gains access by parenteral administration, as in homologous serum jaundice, or by droplet infection or ingestion, as seems probable for spontaneous epidemic jaundice, the resulting hepatitis produces a relatively long disability, the average duration of jaundice in a recent epidemic being approximately 27 days.[25] In most instances a considerable further period of weakness and easy fatigability prevents early resumption of rigorous activity.

The question of the duration of jaundice is of considerable interest with respect to the anatomic type of hepatitis. It will be remembered that Eppinger [5] described two clinical and anatomic (histologic) varieties of hepatitis: (1) the hepatocellular form, (2) the periacinar or cholangitic form. The first of these is generally regarded as the common type, whether sporadic or epidemic. This form, according to Eppinger, is characterized by jaundice of relatively short duration, usually from two to four weeks, with considerable evidence of deranged liver cell function. The second variety is characterized by a more severe jaundice, of much longer duration, commonly two to four months. The liver and spleen are usually enlarged, the stools are acholic and urobilinogen is commonly absent from the urine, at least for long periods. This type obviously offers the greatest difficulty in differential diagnosis, and as Eppinger has pointed out it is a condition in which an operation, carried out with the intention of relieving an extrahepatic biliary obstruction, is likely to be both disappointing and hazardous. The present study has been concerned particularly with cases of this type, which will be referred to henceforth as *cholangiolitic hepatitis*. The reasons for the use of this term are discussed subsequently. A number of illustrative examples are described in the following:

Case Reports

Case 1. D. G., male, aged 18. This patient suffered a brief attack of diarrhea early in December, 1942, shortly followed by an episode of painless jaundice that lasted until June, 1943. At the time of onset he was living with a brother who had had jaundice in August, 1942. The patient was inducted into the Navy in July, 1943, and received yellow fever vaccine during his preliminary training period. He felt well until Nov. 5, 1943, when he had a brief attack of diarrhea; jaundice appeared within a few days. It may be noted, however, that he had observed dark urine since

about October 15. He stated that he had recently heard from his brother, then in the Army, and that he too was ill with a recurrent attack of jaundice. This was subsequently confirmed in a letter from an Army Medical Officer. The patient was admitted to the Medical Service on November 20. He was well developed and well nourished, apparently comfortable but quiet and mildly apathetic. The liver was found to be 5 cm. below the rib margin in the right mid-clavicular line; it was smooth and not tender. The spleen was palpable at times and again it could not be felt.

The patient remained in the hospital until February 7, 1944. Treatment included a high carbohydrate (350 gm.), high protein (150 gm.; 50 per cent meat), low fat (50 gm.), "liver" diet with supplementary vitamin B complex and vitamin C. Decholin * (3 c.c. of a 20 per cent solution) was given twice daily intravenously from December 5 to January 6 inclusive. It was doubtful that this had any effect since bile did not begin to return to the bowel until December 21, a full two weeks after commencement of this therapy. This is seen in the relationships of the serum bilirubin, urine and feces urobilinogen as shown in figure 1. A composite liver function study,[26] carried

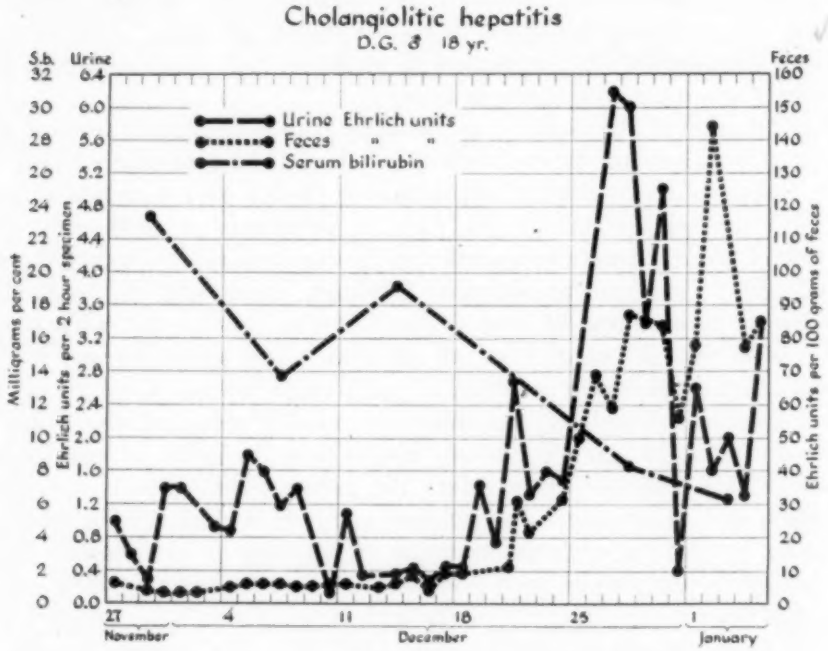


FIG. 1. (*Case 1*) Serial data for serum bilirubin, urine and feces Ehrlich units as obtained in this case of cholangiolitic hepatitis. Evidence of high grade or complete exclusion of bile from the intestine is noted during the first half of the period shown. The relative increase of Ehrlich units in the urine from November 30 to December 11 was interpreted as indicative of hepatic parenchymal damage, which is shown more strikingly during the opening phase from December 18 onward. (Reproduced from the article by Dr. C. J. Watson [27] in the *American Journal of Clinical Pathology*, 1944, xiv, 613; courtesy of Williams and Wilkins Co., Baltimore.)

out between December 8 and 13, revealed a pattern characteristic of a regurgitation jaundice with complete biliary obstruction but with relatively normal liver cell function (see figure 2). The negative cephalin cholesterol flocculation is especially noteworthy.

* Riedel-deHaen, Inc.

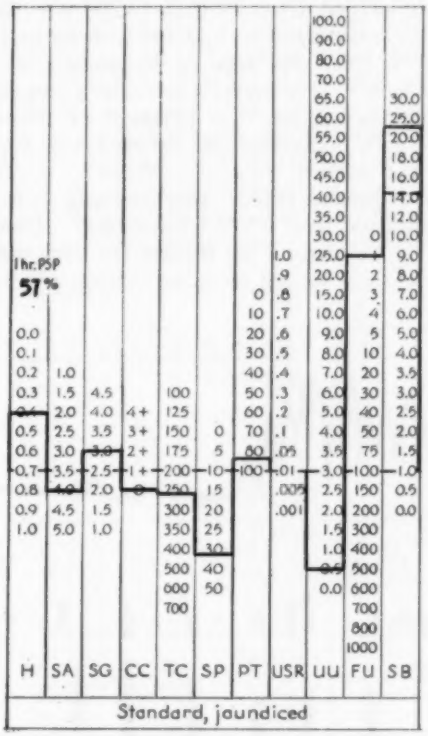


FIG. 2. (*Case 1*) Liver function studies carried out in the period November 21 to 23, 1943, just prior to that shown in figure 1. For column designations in this and subsequent figures, see key.

KEY TO COLUMN DESIGNATIONS IN FIGURES 2, 4, 5, 5, 6, 8, 9, 10, AND 11 (LIVER FUNCTION STUDY CHARTS)

In order to conserve space, the columns for the standard, nonjaundiced and for the supplementary groups of procedures, as included in previously published liver function studies [26] have been omitted from this and subsequent figures.

H Hippuric acid in gm., one-hour urine specimen (1.77 gm. Na benzoate and 6 mg. phenolsulphonphthalein given I.V.).
SA Serum albumin in gm. per 100 c.c.
SG Serum globulin in gm. per 100 c.c.
CC Cephalin cholesterol, 0 to 4+ (read at 24 hours).
TC Total serum cholesterol in mg. per 100 c.c.
SP Serum phosphatase, alkaline, in King-Armstrong units unless otherwise specified.
PT Prothrombin in per cent of normal.
UU Urine urobilinogen in mg. per 24 hours.
FU Feces urobilinogen in mg. per 24 hours.
UE Urobilinogenuria, expressed as Ehrlich units in a 2 to 4 p.m. urine specimen. Upper limit of normal is 1 unit, rather than 3 as appears in the chart.
FE Feces urobilinogen, expressed as Ehrlich units per 100 grams of stool.
SB Serum bilirubin in mg. per cent, upper solid line is total; lower broken line is 1 minute reading.
USR Urine-stool urobilinogen ratio.

Hippuric acid formation is seen to be moderately reduced but it should be emphasized that this is a common finding in cases of marked extrahepatic biliary obstruction when jaundice has been present for more than two or three weeks; in other words a moderate disturbance such as shown in figure 2 cannot be construed to mean that the jaundice is due to a diffuse liver disease rather than to an extrahepatic cause.

The urine contained large amounts of bilirubin, and, as shown in figure 1, varying amounts of urobilinogen, but was otherwise normal. The hemoglobin was 15.3 gm. per 100 c.c. at admission; by December 9 it had fallen to 11.5 but was 13.0 on December

23. The leukocyte count ranged from 9950 to 13,200 with from 66 to 80 per cent neutrophiles. On admission the count was 13,200 with 66 per cent neutrophiles.

A needle biopsy of the liver was done on November 29. The technic employed has been described elsewhere.[26] The sections revealed a surprisingly normal histology in spite of the marked jaundice at this time (Plate I, a). Some bilirubin staining of the central lobular cells with occasional bile thrombi was apparent. The periportal cellular infiltration was not marked.

After December 21, it became evident that bile was returning to the intestine as determined by the quantitative feces Ehrlich reaction.[27] There was progressive improvement thereafter. By February 7 the patient felt very well; there was but slight residual icterus, and he was discharged from the medical service.

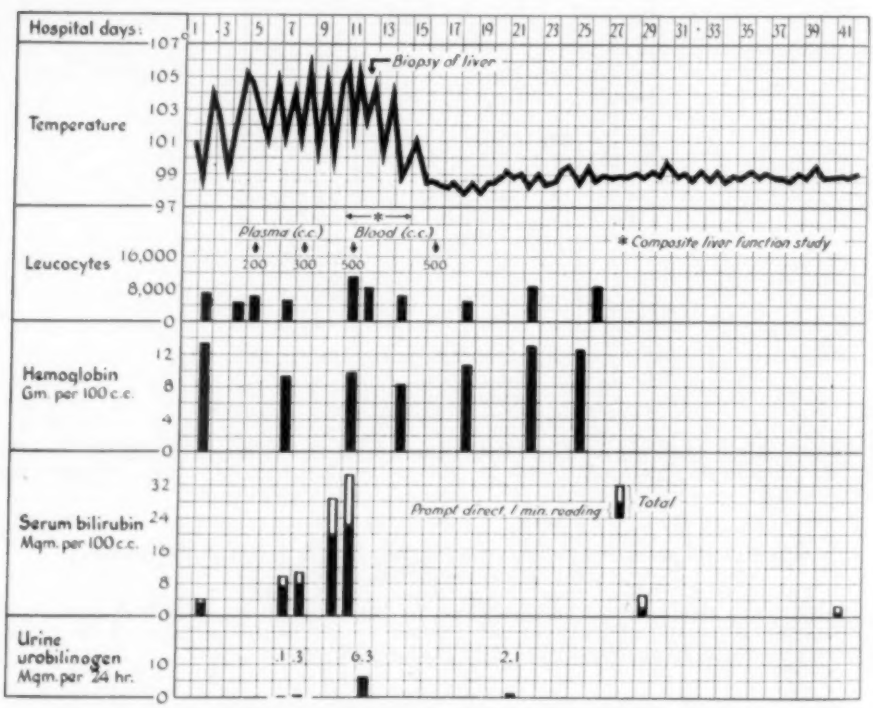


FIG. 3. (*Case 2*) Clinical course of cholangiolitic hepatitis in a 15 year old girl.

Case 2. D. K., female, aged 15. This patient was first admitted on the Pediatric Service * of the University Hospital on July 20, 1943. At this time a right indirect inguinal hernia was repaired. A wound infection occurred and the wound opened and drained; culture of the pus yielded hemolytic streptococci. After further bed rest and sulfonamide therapy the wound healed and the patient was discharged on August 20, 1943. She was readmitted on the Pediatric Service on October 1, 1943, complaining of headache and malaise, nausea, vomiting and fever of about five days' duration. On the day before admission she suffered a chill and the temperature rose to 104° F. Chills and marked fever characterized the hospital course for the first 14 days. The temperature elevation was characterized by daily rises to from 104° to 106° F., the peak usually being reached in the evening, the temperature then falling to nor-

* We are indebted to Dr. Irvine McQuarrie for permission to study this patient and report the findings.

mal or nearly normal levels in the morning (see figure 3). Slight icterus was first noted at the time of admission and it was subsequently determined that early in September, 1943, the patient had stayed in the same house with three children who had mild jaundice. The serum bilirubin on the day following admission was: 1′, 3.4 mg.; total 4.0 mg. The 1′ bilirubin is synonymous with the prompt reacting type, elevation of which is believed to characterize regurgitation as contrasted with retention jaundice. The difference between the total and the 1′ represents the delayed or indirect reacting fraction.[28] The jaundice rapidly deepened and six days later the values were: 1′, 7.98 mg.; total, 10.5 mg. The physical examination at the time of admission revealed nothing of significance other than mild icterus and some lethargy. The liver and

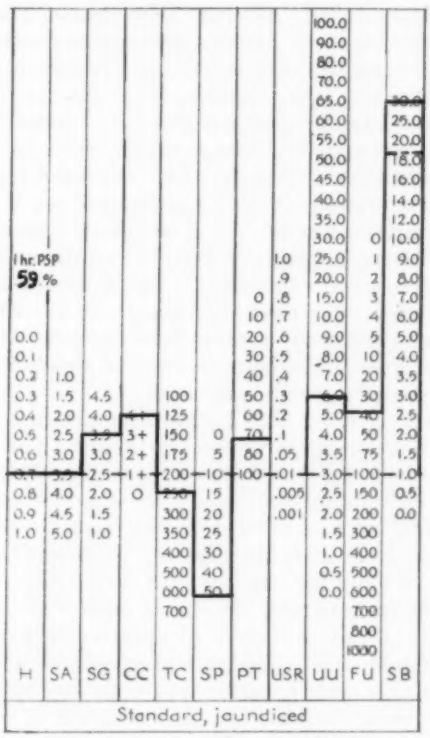


FIG. 4. (*Case 2*) Liver function studies carried out during febrile period indicated in figure 3, October 11 to 14, 1943.

spleen were not palpable. By the fifth day the liver had become palpable 2 cm. below the costal margin; it was not tender, but there was slight tenderness over the herniorrhaphy scar in the right lower quadrant. Duodenal drainage on this date failed to reveal bilirubin and cholesterol crystals were not observed. A moderate number of pus cells was present. At this time the patient developed a diffuse morbilliform, partly urticarial and itching rash which persisted for several days. Various laboratory findings, as related to the fever and other factors, are shown in figure 3. A composite liver function study was carried out during the period indicated. The data obtained are shown in figure 4. It is seen that there is some evidence of liver functional disturbance, including a positive cephalin cholesterol flocculation. The relative lack of urobilinogenuria was rather surprising with so much fever and the evident presence of an appreciable amount of bile in the intestine.

A liver biopsy was carried out with the Silverman needle. Culture and animal inoculation of a portion of the material obtained was negative. The histologic structure is shown in Plate 1, b. Bilirubin staining of the centers of the lobules was noted, together with a moderate number of bile thrombi. Some increase of leukocytes was seen about the portal spaces, although this was not prominent. No necrosis was observed. The pathologist, Dr. J. S. McCartney, concluded that this was either "obstructive or acute catarrhal jaundice."

The temperature had returned to normal by the fifteenth hospital day. It is of some interest that a transfusion of 500 c.c. of whole blood had been given on the eleventh hospital day, on which the temperature twice reached 106° F., once before and once after the transfusion. On the twelfth day an elevation to 105° was noted, on the thirteenth and fourteenth to 102° and 101°, respectively, after which there was no further fever. The patient had been offered the aforementioned "liver" diet, but during the severe fever had eaten but relatively little. However, she received a liter of 10 per cent glucose in distilled water and the same amount in normal saline, given intravenously, each day until her appetite had improved. On the fifteenth hospital day, at the time the temperature returned to normal, the liver was recorded as three fingers'-breadth below the costal margin. From this time forth the patient improved rapidly. On the twenty-ninth day the serum bilirubin had declined to: 1′, 2.4 mg.; total, 5.3 mg. On the forty-first day jaundice was no longer manifest, although the serum bilirubin was still elevated: 1′, 1.1 mg.; total, 2.6 mg. The patient was discharged feeling entirely well on the forty-second hospital day. She was seen again in the out-patient clinic in March, 1944, five months after discharge. At this time she felt quite well, there was no jaundice and the liver and spleen were not palpable. The serum bilirubin was: 1′, 0.2 mg.; total, 0.6 mg. The Hanger cephalin cholesterol flocculation test was recorded as 1 + in 24 hours, 2 + in 48 hours.

Case 3. R. A., male, aged 9. This patient was admitted to the Pediatrics Service of the University Hospital on November 25, 1943.* The mother stated that his illness had commenced during the first week of September, 1943. At this time he had complained of fatigue, malaise and anorexia. He was able to attend school for one week with these symptoms but was so tired that he went to bed as soon as he arrived home each afternoon. A week after the onset of symptoms he developed a moderate diarrhea with occasional vomiting, and it was now observed that the skin was becoming yellow, the urine dark and the stools light. He was seen by the local physician who prescribed certain medicines of undetermined nature, probably a laxative and some form of iron pills. The patient gradually improved and two weeks later was able to return to school, jaundice apparently having disappeared. After he had been in school one week, during which he continued to complain of fatigue and malaise, the jaundice recurred. His condition became worse and he was taken to a private hospital. Shortly thereafter he became irrational and he remained in this state, with occasional lucid intervals, until his admission to the University Hospital three weeks later. On a number of occasions he was violent and difficult to restrain. There were no convulsions. In spite of frequent administration of glucose and saline intravenously, his condition gradually grew worse. During this period there was moderate fever, on but one occasion, however, above 100° F.; this was on November 20 when it rose to 103.8° F. The laboratory record at the private hospital revealed a leukocyte count of 7600 with 77 per cent neutrophiles; the urine at the outset contained 4 + urobilinogen but subsequently gave negative tests. The feces were reported as acholic.

It is worthy of note that a neighbor of the patient's had been jaundiced about one month prior to onset of the patient's symptoms. Two months after the patient's

*We are indebted to Dr. Irvine McQuarrie for permission to study this patient and report these findings.

jaundice was first observed, a little girl in the neighborhood had a similar but much milder attack of jaundice.

On admission to the University Hospital the temperature was 100° F., pulse 120, respirations 26, blood pressure 124 mm. Hg systolic and 100 mm. diastolic. The patient appeared chronically ill, markedly malnourished and in a grave condition. He was conscious but could not talk, responding only by movements of the head. An intense icterus of a golden brown hue was present. A few petechiae and ecchymoses were noted. There was increased tonicity of all extremities with a gross regular tremor of the muscles of the upper extremities, and a fine tremor of the hands. A fetor was observed at this time but no note was made as to whether it was the fetor hepaticus or not. Later on this characteristic fetor was present and outspoken. The abdomen was markedly distended; the superficial veins were prominent. There was bulging in the flanks with shifting dullness and a distinct fluid wave. Because of the marked ascites it was impossible to determine whether the liver or spleen was enlarged. Mild edema of the scrotum and legs was noted. The routine urinalysis on admission revealed only a large amount of bilirubin, no urobilinogen (qualitative Ehrlich test only). The hemoglobin was 12.3 gm. per 100 c.c., leukocytes 10,150 with 71 per cent neutrophiles from 45 to 82 per cent. Unfortunately, the liver function studies in this case were spread out over a long period of time so that it is impossible to depict the composite liver functional status at one time. Nevertheless, a considerable amount of information was gained. During the first several weeks urobilinogen was tested for in the urine and feces only in qualitative fashion. On November 30 the feces urobilinogen was recorded as 1+. Until December 2 the urine Ehrlich reaction for urobilinogen was consistently negative but from the third on it was usually positive. During the period of December 13 to 17 the feces urobilinogen was determined to be 47.8 mg. per day. The serum bilirubin values during the hospital course were as follows:

Date	Serum bilirubin in mg. per 100 c.c.	
	1′	Total
11–25–43	20.3	33.8
12–13–43	27.6	35.9
12–28–43	13.6	23.9
1–3–44	7.4	16.4
1–11–44	6.2	12.5
1–31–44	2.7	5.6
3–15–44	0.5	1.0

On January 31 the 2–4 p.m. urine sample contained 4.4 Ehrlich units * and on February 3, 4.8 Ehrlich units. As already noted the qualitative test for urobilinogen was quite consistently positive both before and after these dates, except for the first week after admission.

The total proteins of the serum were determined repeatedly, but unfortunately, a fractional study was not carried out at any time. The values for total serum protein in gm. per 100 c.c. on different dates were as follows: 11–25–43, 5.7; 12–8–43, 5.4; 12–28–43, 5.3; 1–11–44, 7.6; 1–31–44, 8.7; 3–15–44, 8.0. In relation to these values it may be noted that there was no recurrence of ascites or edema after January 10. It is quite evident that a striking improvement in protein formation occurred between 12–28–43 and 1–11–44. The cephalin cholesterol flocculation in 24 hours was recorded as follows for the dates given: 12–14–43, 4+; 1–14–44, 4+; 2–11–44, 4+; 9–11–44, 2+. It may be noted that with improvement the sedimentation velocity in-

* Normal upper limit: 1 unit.[27]

creased, from 15 mm. in 60 minutes on 11–27–43 to 113 mm. on 2–14–44; it was still 50 mm. on 6–15–44, although the jaundice and ascites at this time had long since disappeared. The prothrombin time and response to vitamin K were markedly abnormal The values are given in the following:

11–27–43	28.4″	(control 16.7″)
11–30–43	35.2″	(" 19.6″)
12–3–43	29.9″	(" 18.5″)
12–7–43	22.4″	(" 16.1″)
12–13–43	20.3″	(" 17.1″)
1–5–44	32.8″	(" 19.9″)
1–11–44	25.2″	(" 18.4″)
1–28–44	16.1″	(" 15.5″)
3–15–44	22.0″	(" 21.6″)
6–10–44	13.2″	(" 11.6″)

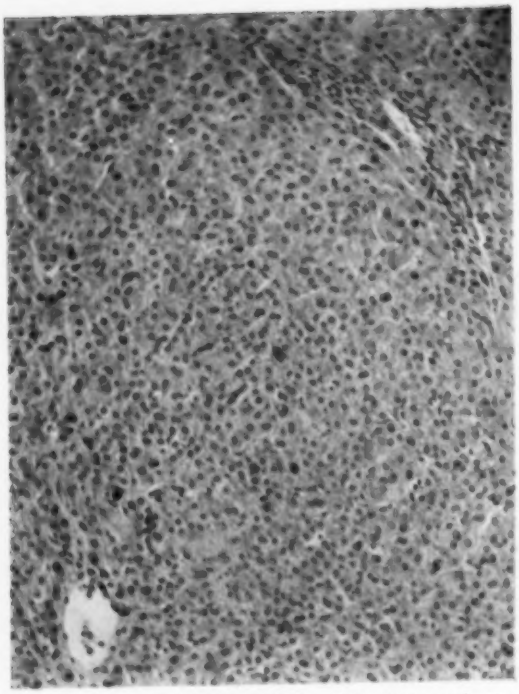
With relation to the above data it may be noted that vitamin K * was given intramuscularly each day from admission through January 3, 1944. During the same period the patient received almost daily infusions of human plasma ranging in amount from 150 to 300 c.c. (usually 150 to 200). From December 11 to 20 there was an otitis media which caused daily elevations of temperature to 103 to 104° F. This infection subsided spontaneously. The patient was released from the hospital on January 14, much improved, although not ready for discharge; the release was necessitated by a labor strike against the hospital. He was readmitted on January 29 for further study. At this time the ascites had entirely disappeared. The liver edge was palpable about 6 cm. below the costal margin on the right, and the spleen was easily palpable. On February 8, 1943, a liver biopsy was performed with the Silverman needle. The histologic structure is seen in Plate 1, c. The report of the pathologist, Dr. J. S. McCartney, was as follows: "There is a distinct increase in the portal connective tissue but little if any increase in the number of bile ducts. In the portal tissues there is a mild degree of lymphocytic infiltration. There are fairly numerous dilated bile capillaries and bile thrombi. Most of these are central. A rather large number of liver cells are multinucleated. There are no signs of necrosis or fatty metamorphosis."

At the time of discharge on February 17, 1944, the patient had a good appetite and was gaining weight. Jaundice was no longer manifest. On March 17 the total serum bilirubin was at the upper limit of normal, but it is noteworthy that the 1′ (prompt) bilirubin was still considerably elevated (0.5 mg. per cent). Recent studies [63] have shown that the upper limit of normal for the 1′ bilirubin probably but rarely exceeds 0.2 mg. per 100 c.c. The liver and spleen were still palpable on August 12, 1944. When he was last seen in the out-patient clinic on Sept. 11, 1944, the cephalin cholesterol flocculation was 2 + in 24 hours, 3 + in 48 hours, and the 2–4 p.m. urine sample contained 1.3 Ehrlich units (upper limit of normal 1.0 unit).

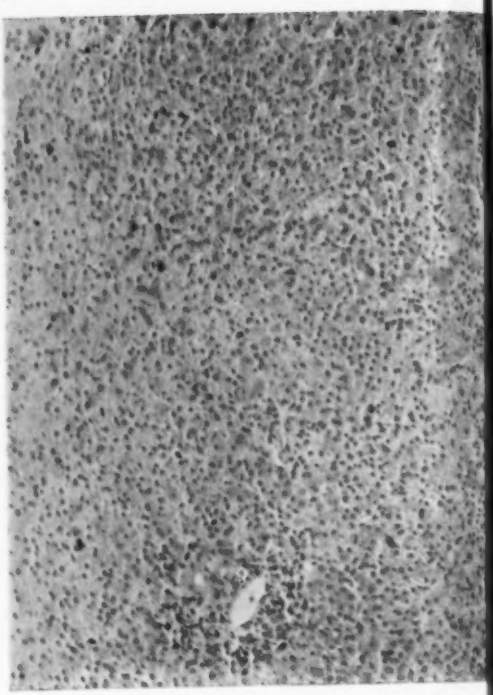
Case 4. V. E., male, aged 29. This patient was admitted to the Medical Service of the University of Minnesota Hospital on October 11, 1944. Ten weeks prior to admission he had noted marked anorexia, nausea, and some vomiting; at the same time his upper abdomen was "sore to touch," especially on the right side. Two days after the onset of these symptoms he observed that his eyes were yellow. The jaundice deepened rapidly and was accompanied, almost from the first, by pruritus. The stools were light in color, the urine dark. Treatment by the local physician consisted of intravenous glucose and saline, together with bile salts and vitamin K by mouth. After the first week the nausea and vomiting disappeared and the appetite improved somewhat. In spite of this, however, there was a weight loss of approximately 30

* Hykinone 4. mg. (Abbott Laboratories, Inc.)

PLATE I



I A. Case 1. Cholangiolitic hepatitis. Microscopic appearance of liver biopsy secured on Nov. 29, 1944, during period of complete suppression of bile flow. The histology is surprisingly normal. Bilirubin staining is observed around the centers of the lobules. Hematoxylin and eosin × 90.



I B. Case 2. Cholangiolitic hepatitis. Microscopic appearance of liver biopsy secured during febrile period shown in figure 3. Bilirubin staining of central lobular cells with occasional bile thrombi. Mild periportal cellular infiltration. Hematoxylin and eosin × 90.

I C. Case 3. Cholangiolitic hepatitis with probable early cirrhosis. Microscopic appearance of liver biopsy secured 5 months after the onset of jaundice. Increase in portal connective tissue and mild lymphocytic infiltration. Multi-nucleated liver cells are common. Hematoxylin and eosin × 110.

I D. Case 6. Cholangiolitic hepatitis. Microscopic appearance of liver biopsy secured at operation 5 months after onset of jaundice. Moderate periportal lymphocytic infiltration. No fibrosis. Some multi-nucleated liver cells. Central bilirubin staining. Hematoxylin and eosin × 90.

pounds in the 10 weeks prior to admission. Further history was obtained that about one month before the onset of the above symptoms and jaundice, the patient was on a house party with eight other persons, including his wife. One of the other women in the group was mildly jaundiced and sufficiently ill to consult a physician in a small town near the summer home where the party was in progress. Of the other eight persons, four including the patient and his wife, subsequently became jaundiced. The wife's jaundice, however, disappeared in about 10 days, after which she recovered rapidly. The course of the disease was similarly mild in the others, except for the patient whose jaundice, as already noted, deepened progressively. In addition to the five persons in the group who became ill, it was determined that the small son and the sister of one of the jaundiced women later developed nausea, vomiting and icterus of relatively brief duration. It was of interest that the patient's daughter did not become sick or jaundiced.

Examination in the hospital revealed a well developed, deeply jaundiced, emaciated white male. The weight was 119 lbs. There was no temperature elevation, either upon admission or later. The blood pressure was 110 mm. Hg systolic and 60 mm. diastolic, pulse 56, regular rhythm. A mild fetor hepaticus was noted on the breath. The liver edge was easily palpable in the right mid-clavicular line at the level of the umbilicus. The spleen was barely palpable. No spider nevi were observed. There were many excoriations. Mild edema of the ankles was present.

The hemoglobin on admission to the hospital was 8.8 gm. per 100 c.c., the red blood cells 3,250,000 per cu. mm. Within a week the hemoglobin had fallen further to 7.1 and the erythrocytes to 2,850,000. The leukocytes ranged between 6100 to 11,200 with from 50 to 71 per cent neutrophiles. Routine urinalysis revealed nothing abnormal except for the presence of bilirubin. The results of the composite liver function study are shown in figure 5. This revealed very little evidence of hepatic functional derangement, the only changes being in the failure of hippuric acid to appear in the urine after intravenous sodium benzoate, together with the lack of any elevation of cholesterol in spite of a marked regurgitation jaundice (1′ bilirubin of 18.8 mg. with large amounts of bilirubin in the urine; pruritus). It is of interest that the total cholesterol value rose appreciably as the patient improved and as the jaundice diminished. In table 1 the serum cholesterol values are correlated with the serum bilirubin values and with those for the Ehrlich reaction in urine and feces. The intake of food was exceptionally good, ranging from 2500 to 4000 calories per day, not including 400 calories contributed by 1000 c.c. of 10 per cent glucose in distilled water which was given daily throughout the entire hospital stay. This solution contained 25 units of crystalline insulin which was included not with the idea of improving utilization of glucose, but because the administration of this mixture has been noted, in certain instances, to be followed by an increased appetite. During this entire period the patient received the low fat "liver" diet as described in the foregoing. A whole blood transfusion of 500 c.c. was given on Oct. 28, 1944, Nov. 21, 1944 and Nov. 26, 1944. At the time of discharge the hemoglobin was 16.7 gm. per 100 c.c. and the erythrocytes were 5,060,000 millions per cu. mm.

Liver biopsy was carried out in this instance on October 17, about 11 weeks after the onset of jaundice and just after completion of the liver function study shown in figure 5. The amount of liver obtained was relatively small, representing portions of but three lobules. Bilirubin staining was prominent, especially toward the periphery of the lobules. Quite a number of multinucleated liver cells were seen in the same areas. There was no necrosis, leukocytic infiltration, fibrosis or bile duct proliferation.

This patient was last seen on December 12, 1944, at which time he felt very well, although mild icterus was still evident. His appetite was good. The liver and spleen were not palpable.

Case 5. E. L., housewife, aged 51. The patient was admitted to the Medical

Service of the University Hospital on September 15, 1944. Her illness commenced with nausea and vomiting about July 4, 1944. At this time she felt cold and thought she had some fever, but there were no definite chills. Within a few days she became jaundiced and noted that the urine was dark and the stools light in color. The jaundice deepened and was associated with itching from the outset. There was no pain at any time, nor any history suggestive of gall stones. With the onset of nausea and vomiting a marked anorexia developed, especially characterized by distaste for fatty foods. The patient suffered a weight loss of 20 pounds prior to admission to the hospital. She stated that the jaundice and itching had become somewhat less but that the vomiting persisted.

TABLE I

Laboratory Data Relating to Jaundice and Serum Cholesterol in Case 4 (V. E., Male, 29)

Date	Ehrlich units Urine 2–4 p.m. sample	(urobilinogen) Feces (per 100 gm.)	Serum bilirubin in mg. per 100 c.c.		Serum cholesterol in mg. per 100 c.c.
			1′	Total	
10–12–44	0	16.8	18.8	34.6	183
10–16–44	0				
10–17–44	0				
10–19–44	0				
10–23–44	0.3				
10–27–44	0.9				
10–28–44		9.6	10.1	18.3	
10–30–44	1.0	8.4			
10–31–44			5.4	8.8	182
11–1–44	3.8				225
11–2–44	3.7				
11–3–44	0.8				
11–6–44			4.2	7.0	
11–9–44	0.9				
11–14–44	1.0				
11–17–44		56.0			
11–19–44	2.3		2.4	2.9	
11–20–44	2.09				330
11–21–44	1.4		1.2	2.5	312
11–22–44	1.5				
11–23–44		7.20			
11–24–44	2.4				
11–27–44	2.2	88.0			289
11–28–44		160.0	0.9	2.1	
11–29–44	1.0	104.0			

Examination revealed moderate jaundice with numerous excoriations of the skin. The liver edge was easily palpable 1 to 2 cm. below the right costal margin. It was not tender. The spleen was not palpable. Examination of the blood revealed a hemoglobin of 9.45 gm. per 100 c.c., erythrocytes 4,090,000, leukocytes 5050 to 8350 with from 52 to 79 per cent neutrophiles, usually less than 60. The sedimentation velocity was 64 mm. in 60 minutes. The results of the composite liver function study are shown in figure 6. This reveals distinct, although variable, evidence of functional derangement in the presence of regurgitation jaundice; (bilirubinuria and increased 1′ serum bilirubin). It may be noted on the basis of the feces urobilinogen, that the element of obstruction or exclusion of bile from the intestine was relatively slight. The stools at this time, of course, were no longer acholic in appearance.

Liver biopsy was done on Oct. 3, 1944, at the time of peritoneoscopy, using a modified Silverman needle as described elsewhere.[26] The appearance of the surface of

the liver was normal. The piece of liver obtained consisted of portions of seven or eight lobules (plate 2a). In the main the liver architecture was relatively normal. In one area, not shown in the plate, a small amount of periportal fibrosis and lymphocytic infiltration was observed. Scattered bile thrombi, together with occasional atypical, multinucleated liver cells, were also seen. At this time the patient had been in bed and receiving the "liver diet" for 18 days. The serum bilirubin on Oct. 6, 1944, three days later, had decreased to: 1′, 1.3 mg.; total, 2.5 mg. per 100 c.c. It may be noted that a cholecystogram on Oct. 7, 1944, revealed a non-functioning gall-bladder without evidence of calculi. The itching had disappeared and the patient felt considerably better. She was allowed to go home on Oct. 12, 1944, with instructions to

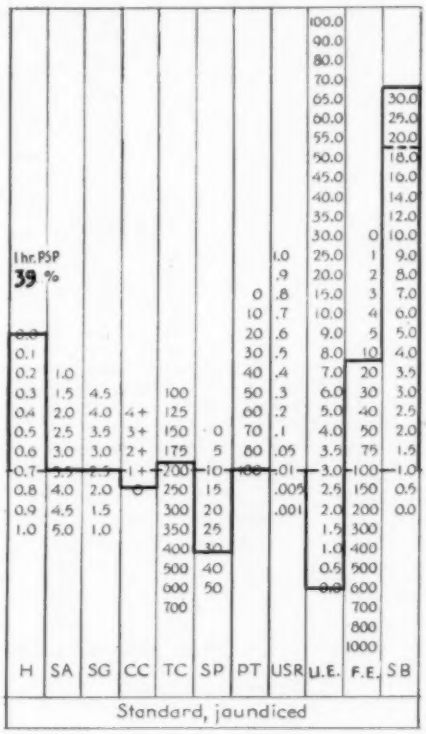


FIG. 5. (*Case 4*) Liver function studies carried out during height of patient's jaundice, October 12 to 17, 1944.

continue rest, to adhere to the "liver diet" and to take vitamin B complex, two capsules three times daily. She returned on November 1 stating that she felt very well. The liver and spleen were not palpable. There was still slight icterus, however, and if anything, the serum bilirubin had risen slightly: 1′, 1.2 mg.; total, 2.8 mg. per 100 c.c. The patient was again seen on November 29 still feeling very well but slightly jaundiced. She was readmitted to the hospital February 6, 1945. At this time she still exhibited a mild jaundice. Pruritus had become severe and the patient's appetite was poor. Physical examination failed to reveal any appreciable change; the liver was not enlarged, the spleen was not palpable. Neither palmar erythema nor spider nevi were seen. Roentgen-ray examination of the esophagus failed to reveal any evidence of varices. A composite liver function study (see figure 7) revealed little change

from that of her previous admission. A moderate reduction of hippuric acid formation is noted, and the total cholesterol is seen to be increased over that of the previous admission. The patient was offered a high protein, high carbohydrate diet but ate very little. Ten grams of methionine * in 1000 c.c. of distilled water containing 10 per cent glucose were given intravenously daily, for seven days, without noticeable benefit.

Despite the evidence favoring a parenchymal type of liver involvement, the possibility of a silent common duct stone could not be excluded with certainty. Therefore, on March 6, 1945, a laparotomy was performed; the gall-bladder and bile ducts were found to be entirely normal. A cholangiogram was made and no obstruction in the

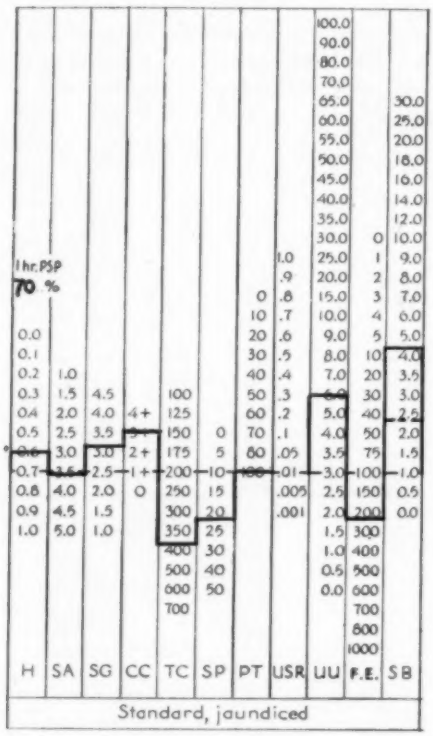


FIG. 6. (*Case 5*) Liver function studies carried out September 25 to October 7, 1944, during the first hospital admission. The urine urobilinogen values shown represent the average of three daily determinations.

extrahepatic biliary tract was discovered; the biliary tree in the liver was well demonstrated. Liver biopsy and cholecystostomy were performed. The latter procedure was done with the purpose of interrupting the enterohepatic circulation of bile-salts in the hope of relieving the severe pruritus. As a matter of fact the patient did experience marked relief from the operation. In addition to relief from the pruritus the appetite improved and the patient gained weight. Subsequently, the tube, which had been in the gall-bladder, came out, and following this the patient's itching recurred.

The liver biopsy on March 6, 1945 (plate 2b), revealed the following histological changes: "the capsule was not thickened; all of the portal spaces were enlarged but none had coalesced; there was a mild increase of the portal connective tissue and a

* Provided through the courtesy of John Wyeth and Brother, Philadelphia, Pa.

marked increase in the number of the ducts with rather marked increase in the number of lymphocytes. The liver cell cords show no appreciable change; no bile thrombi were seen." Dr. McCartney's conclusion was "mild cirrhosis." Some of the cholangioles in this biopsy appeared abnormal, exhibiting swelling.

Case 6. P. N., male, aged 69, laborer. The patient was admitted to the Medical Service of the University of Minnesota Hospital on February 4, 1944. He complained principally of intense pruritus; this had commenced in September, 1943, and gradually increased in severity. Jaundice was noted first in November. It was painless in onset and had gradually increased in intensity. The patient denied any history of abdominal pain, nausea or vomiting in relation to the present illness. There was no

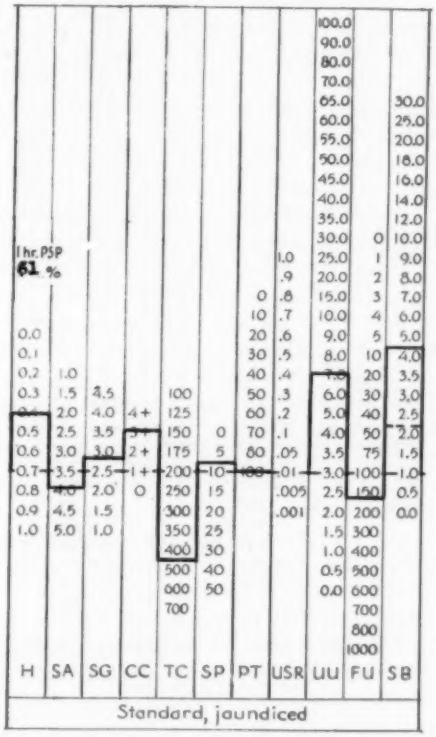


FIG. 7. (*Case 5*) Liver function studies carried out, February 7 to 9, 1945, during second hospital admission before cholecystostomy was performed. In this instance the phosphatase value (S.P.) is expressed in Bodansky units.

history of alcoholism, no exposure to known hepato-toxins, nor contact with other cases of jaundice. The appetite had remained good; nevertheless, a 10 pound loss of weight had occurred over a six month period. A review of the past history revealed nothing of significance.

Physical examination revealed a well developed and well nourished male of the stated age. Moderately severe jaundice was visible; the entire body was involved by excoriations secondary to the pruritus. No other abnormalities were detected. Repeated subsequent examinations of the abdomen failed to reveal the presence of an enlarged gall-bladder. The liver and spleen were not enlarged. The routine examination of the urine disclosed no abnormality other than the presence of bilirubin.

The Kline test for syphilis was negative. The hemoglobin was 11.25 grams per 100 c.c., the erythrocytes numbered 3.58 millions per cu. mm.; the leukocyte count was 7800 with 64 per cent neutrophiles, 25 per cent lymphocytes, 5 per cent monocytes, 5 per cent eosinophiles and 1 per cent basophiles. The erythrocyte sedimentation velocity was 68 mm. in 1 hour. The stools were said to be acholic in appearance. A roentgen-ray examination of the gastrointestinal tract revealed no evidence of intrinsic disease. The clinical impression was probable neoplastic obstruction of the extrahepatic biliary tract. The results of the composite liver function study are given in figure 8. This revealed that the degree of biliary obstruction was incomplete since

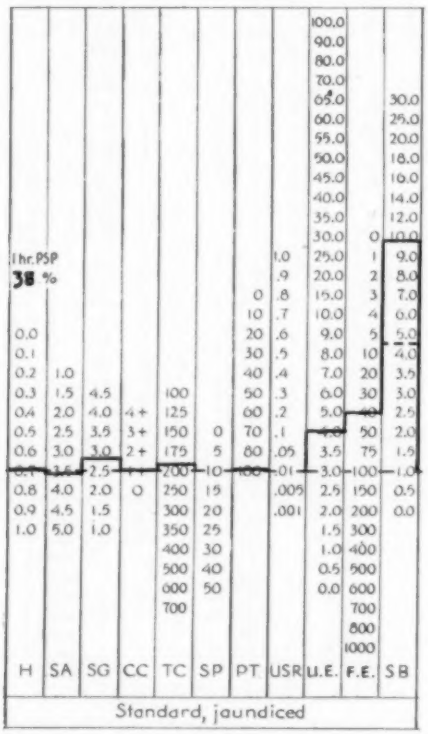


FIG. 8. (*Case 6*) Liver function studies during period of preoperative investigation, February 6 to 11, 1944. The urine Ehrlich values represent averages of five daily determinations.

on two occasions urobilinogen was demonstrated in the feces, though the amount (40 Ehrlich units per 100 grams) was considerably less than normal.[27]

There was little from the laboratory standpoint in this case to suggest parenchymal hepatic disease as the cause of jaundice, certainly no more than one might anticipate in an individual with extrahepatic biliary obstruction of several months' duration. Of particular interest was the cephalin cholesterol reaction graded 1+ and 2+, the excretion of 0.7 gm. hippuric acid in one hour and the normal prothrombin time. A pre-operative diagnosis of extrahepatic biliary obstruction was made. Because of the incomplete degree of obstruction, carcinoma of the ampulla of Vater was strongly considered. In favor of this was the presence of a strongly positive guaiac test for occult blood in the feces. Liver biopsy was not undertaken because of the lack of a palpable liver.

The patient was transferred to the Surgical Service and an exploration of the common bile duct was performed by Dr. Richard Varco. The gall-bladder was small and not distended. The common bile duct was not dilated. The duct was explored and found to be patent throughout its course. A T tube was inserted into the duct and brought to the surface through a stab wound. Two biopsies of the liver were made.

Postoperatively the amount of bile draining to the outside averaged only about 50 to 75 c.c. daily. The degree of jaundice remained essentially the same as it had been preoperatively, and it is worthy of note that the pruritus persisted.

Study of the biopsy of the liver (plate 1d) was reported by Dr. J. S. McCartney to show no increase in portal connective tissue. An excessive number of leukocytes was present in the portal spaces. Scattered bile thrombi were noted, mostly in the regions of the centers of the lobules. The central liver cells were pigmented by bilirubin. Some multinucleated cells were noted. In general the preservation of the normal structure was surprising.

One month after the common duct exploration, a cholangiogram was performed. This revealed good filling of the common duct and the gall-bladder. Some of the intrahepatic branches of the bile ducts were visible. Good drainage into the duodenum was apparent in 15 minutes. The serum bilirubin at the time of the cholangiogram was 6.9 mg. per 100 c.c. of which 5 mg. was the prompt direct (1′) reacting bilirubin. Stool examination at this time revealed 30 Ehrlich units per 100 grams. Analysis of a four day collection of feces immediately prior to this had shown 21 mg. of urobilinogen per day. At the time of discharge from the hospital on April 15, 1944, the patient appeared much the same as when first observed, the pruritus and icterus persisting. He was instructed to continue rest and the "liver" diet at home and to return to the out-patient clinic for follow-up examinations. The T tube was removed in May, 1944, three months after its insertion; jaundice was still evident. By August, 1944, the visible jaundice had disappeared although the serum bilirubin value was still 1.9 mg. per 100 c.c., of which 0.6 mg. was the 1′ type. By September, 1944, the serum bilirubin was normal, the pruritus had largely disappeared and the patient felt well.

This patient had pruritus lasting one year (September, 1943, to September, 1944) and had been jaundiced for 10 months (November, 1943, to August, 1944). During all of this time he felt fairly well, was free of pain, had a good appetite and lost relatively little weight. No benefit was derived from the surgical exploration and the external biliary drainage insofar as the patient was concerned. This case truly bears out the statement made by Rolleston[29] 40 years ago, "Occasionally cases, which begin like ordinary catarrhal jaundice and eventually clear up, hang fire and last for months." It is true that the onset in this instance was somewhat unlike the ordinary case in that the pruritus was present for about two months before the jaundice was noted.

Case 7. F. R., male, aged 47. This patient came under observation in June, 1943, through the courtesy of Drs. J. E. Meyer and M. C. James of Columbus, Nebraska. His complaints were those of pruritus, mild jaundice and fatigability. The pruritus had been present for about four years. It was relatively mild in character and had not caused much discomfort. Jaundice was first noted in October, 1942, when the patient consulted his physician for removal of a xanthoma of the eyelid. Because of the persistence of the jaundice, an exploratory laparotomy was performed and the gall-bladder was drained. No stones were found in the gall-bladder or in the extrahepatic biliary tract. Biopsy of the liver was performed. This was reported as indicating a hepatitis. Drainage of the gall-bladder failed to influence the jaundice or pruritus.

Physical examination in June, 1943, revealed a well developed, well nourished male of 47. Apart from a slight icterus there were no apparent abnormalities. Care-

ful examination failed to reveal the presence of xanthomata or of vascular nevi. The liver was slightly enlarged, the firm edge could be felt just below the costal margin on deep inspiration. The spleen was not palpable.

The hemoglobin was 14.4 gm. per 100 c.c. The leukocytes were 6900 per cu. mm. with 72 per cent neutrophiles. The reticulocytes were 0.6 per cent. The composite liver function study revealed some evidence of impairment (figure 9). Unfortunately the cephalin cholesterol flocculation was not determined at this time, although it was found to be negative three months later in spite of persistence of the other findings.

The patient was observed again in September, 1943. The physical findings were essentially unchanged. The blood cholesterol was again found to be elevated, 449 mg.

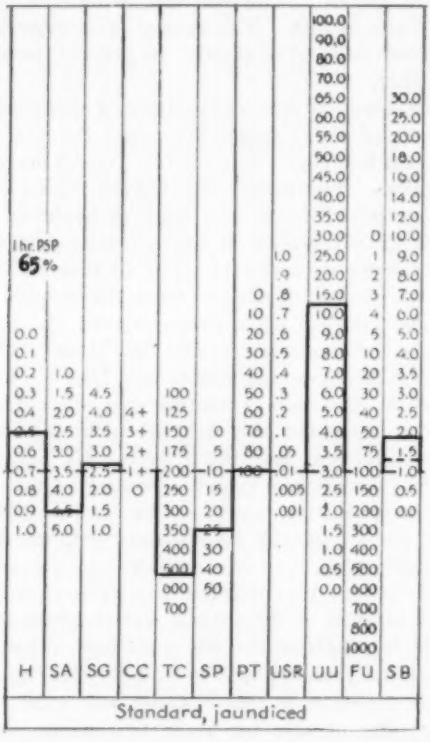
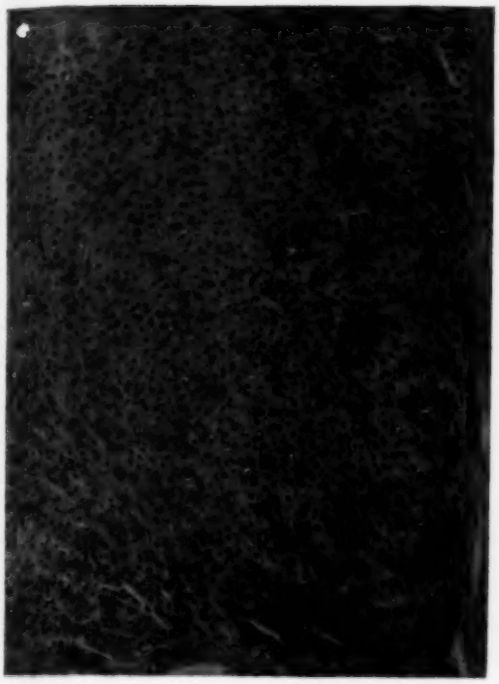


FIG. 9. (*Case 7*) Liver function studies, June 16 to 18, 1943, performed nine months after jaundice was first noted by the referring physician.

per cent. The cephalin cholesterol flocculation test was negative. The bromsulfalein test revealed 19 per cent retention of the dye (20 minutes after injection of 2 mg. per kilo body weight). The 24 hour urine urobilinogen was also distinctly increased, a value of 8.3 mg. being recorded at this time.

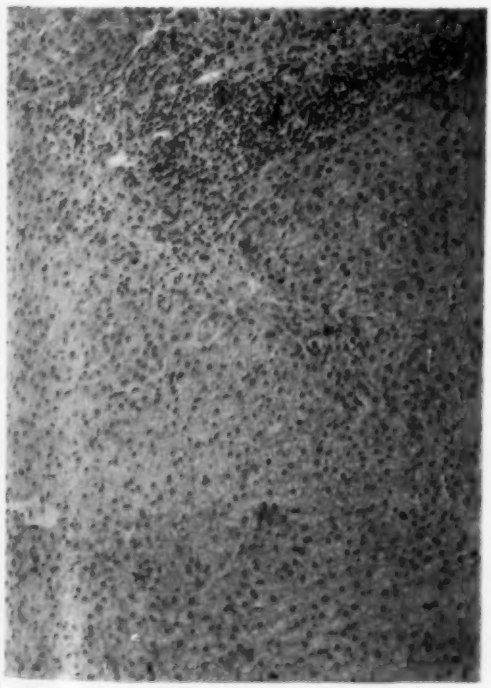
Through the courtesy of Dr. C. B. Baker of the Nebraska Methodist Hospital, Omaha, Nebraska, a section of the liver biopsy obtained at the time of operation by Dr. James in 1942, became available to us. This was stained with hematoxylin and eosin. Dr. McCartney's report on this section was as follows: "Some increase in portal connective tissue. There is a fairly marked degree of lymphocytic infiltration. There are a few polymorphonuclear leukocytes and eosinophiles. There is some increase in fibrous tissue and also in the bile ducts. Most of the lobules appear abnor-

PLATE II

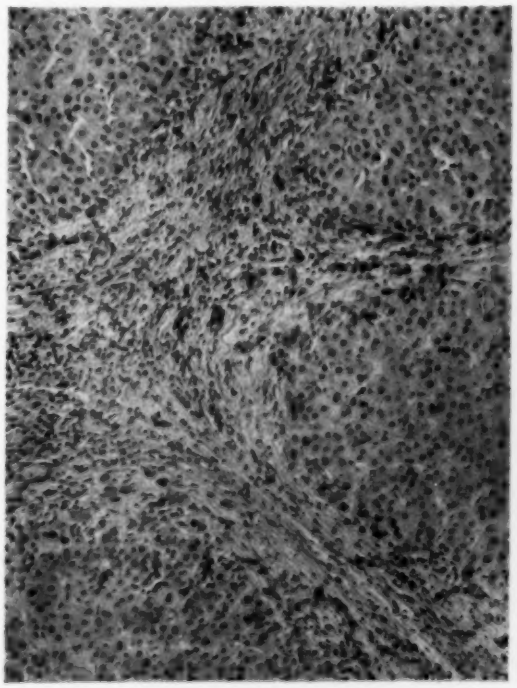


II. A. Case 5. Cholangiolitic hepatitis. Microscopic appearance of liver biopsy secured during peritoneoscopic examination Oct. 3, 1944. Relatively normal histology. Occasional bile thrombi; occasional multi-nucleated liver cells. Portal spaces and evidence of cholangiolitis not shown in this section. Hematoxylin and eosin × 110.

II B. Case 5. Cholangiolitic hepatitis and early cirrhosis. Microscopic appearance of liver biopsy secured at the time of operation (cholecystostomy) March 6, 1945. Portal lymphocytic infiltration and mild fibrosis. Bile duct proliferation and swelling. Multi-nucleated liver cells. Hematoxylin and eosin × 90.



II C. Case 8. Cholangiolitic hepatitis and early cirrhosis. Microscopic appearance of liver biopsy secured at operation in 1936. Marked periportal lymphocytic infiltration with mild increase in portal connective tissue and new bile ducts. Some of these are swollen and have atypical epithelium. Hematoxylin and eosin × 90.



II D. Case 8. Cholangiolitic hepatitis and cirrhosis. Microscopic appearance of liver biopsy secured at operation in 1945. The cirrhosis is seen to be well developed as contrasted with the appearance in 1936 (II C). Extreme portal fibrosis and lymphocytic infiltration; bile thrombi. Hematoxylin and eosin × 90.

mal. No signs of necrosis or proliferation of liver cells can be made out. Conclusion: Early cirrhosis of the liver."

Case 8. C. Q., female, aged 48. This patient was first studied on the Medical Service of the University of Minnesota Hospitals between April 9, 1943, and June 1, 1943. In September, 1944, she was readmitted for a period of one week of observation. Her third admission began April 16, 1945; she was discharged on June 2, 1945. At the time of the first admission the patient complained of weakness, epigastric discomfort, and occasional bouts of diarrhea. Review of her history disclosed that she had had jaundice more or less continuously since the age of 15. This was characterized by recurrent episodes of deeper jaundice, with dull aching right upper quadrant pain. The patient did not use alcohol in any form; her dietary intake was normal.

In 1912 this patient, then 15 years of age, was severely jaundiced during an illness which was characterized by high fever and a prolonged period of disability. Her sister also had jaundice at that time although her symptoms were milder in nature. As nearly as can be ascertained this illness was a severe form of infectious hepatitis (acute catarrhal jaundice). In 1932 during her fourth and last pregnancy the patient was more markedly jaundiced during the last seven months; anorexia and nausea were prominent. In 1936 she consulted Dr. M. O. Oppegard of Crookston, Minnesota, who has kindly made available his observations and surgical findings. Examination at this time revealed that the liver was much enlarged and firm; splenomegaly was noted but there was no evidence of ascites. Roentgen-ray studies revealed a non-functioning gall-bladder. After a period of observation cholecystectomy was decided upon, as offering the patient some hope of relief of the recurrent discomfort. At operation Dr. Oppegard found an enlarged liver exhibiting a definite hobnailed surface. The spleen was enlarged to about three times its normal size. The gall-bladder was found to be thick walled and firmly adherent to the fossa; it contained no stones. A biopsy of the liver was made and a cholecystectomy was performed. The patient made an uneventful recovery and appeared for a time to be relieved of some of her distress. The liver biopsy section was made available to us through the courtesy of Dr. Kano Ikeda, Pathologist at the Miller Hospital, St. Paul, Minnesota. A photomicrograph is shown in plate 2c.

One year later, in 1937, the patient was subjected to a second operation at which a Talma-Morrison omentopexy was performed by Dr. J. F. Malloy at Thief River Falls, Minnesota. The report of this operation was made available to us by Dr. Edward Bratrud of Thief River Falls. It was found that the liver was enlarged, the right lobe extending to the iliac crest; the spleen was enlarged to one and one-half times the normal size. The patient's recovery was uneventful after this operation. She continued, however, to have varying degrees of jaundice. The patient was able to perform most of her household duties, being incapacitated only during periods of more marked jaundice and distress.

In 1943, during the first period of study by us, the outstanding features on physical examination were the massively enlarged liver and the presence of minimal icterus. Ascites was not demonstrable, nor were any spider nevi observed. A faint but definite fetor hepaticus was repeatedly discernible; this was confirmed by several observers. A clinical diagnosis of Hanot's cirrhosis was made. Numerous liver function tests were carried out in serial fashion at this time. The initial observations are shown in figure 10. These reveal obvious evidence of hepatic functional impairment. During this first period of hospitalization, the patient received the "liver diet" and supplements of choline and cystine for a period of six weeks. Although subjective improvement occurred, no significant change in liver function was noted as measured by serial tests. She was allowed to return home on the same diet, but without the choline and cystine. The diet was supplemented by yeast powder and vitamin B complex. This regime was followed for the ensuing year; frequent clinic visits permitted further clinical and laboratory observations.

In September, 1944, the patient experienced a severe attack of right upper quadrant pain associated with nausea and vomiting, chills and fever. The pain was sufficiently severe to require morphine for relief. Jaundice increased at this time and for a short period, acholic stools were noted. The patient was readmitted to the hospital 10 days after this episode. The acute phase had subsided. This episode was entirely similar to what Naunyn and Umber [30] observed in certain cases of cirrhosis and designated as "cholangitis cirrhotica." The cause was assumed to be a secondary (hematogenous) infection of the intrahepatic bile ducts as a sequel to the biliary stasis produced by the fibrosis in the portal spaces. The possibility exists, however, that

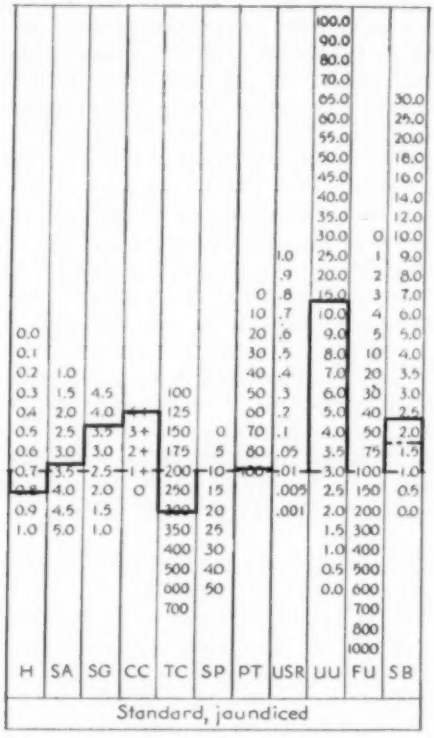


FIG. 10. (*Case 8*) Studies carried out April 15 to 24, 1943, during initial hospital admission. The urine urobilinogen value shown represents average of three daily determinations. Repeated bromsulphthalein tests (2 mg. per kilo dose) showed 6 to 8 per cent retention at 20 minutes during this period of study.

such episodes in some cases are simply exacerbations of the original hepatitis. The history in case 8 would lend support to such a theory, proof of which would have to depend upon demonstration of the presence of the virus. Physical examination disclosed a more marked degree of jaundice (total serum bilirubin of 4 mg. per cent) and a moderate degree of hepatic tenderness. Other findings, clinical and laboratory, were much the same as before. The blood cholesterol level was 440 mg. per 100 c.c. Urobilinogen was constantly present in the urine in abnormal amount. Duodenal drainage failed to reveal any pus cells or crystals. A mild normocytic and normochromic anemia had developed since her previous admission. After a week in the hospital, the patient was allowed to return to her home.

In April, 1945, the patient again returned to the hospital for her third admission. At this time the jaundice was quite intense, and she complained bitterly of pruritus. Physical examination revealed marked jaundice. The nutrition was well maintained. Excoriations of the skin were prominent. Neither spider nevi nor palmar erythema were noted. A definite fetor hepaticus was again observed. The liver measurements were essentially as in 1943 (9 cm. in right midclavicular line, 15 cm. in the midline, and 8.5 cm. in left midclavicular line). The edge of the spleen was palpable 4 cm. below the left costal border. The patient was afebrile; the leukocyte pattern was normal. The mild anemia (hemoglobin 10 grams) was still normocytic and normo-

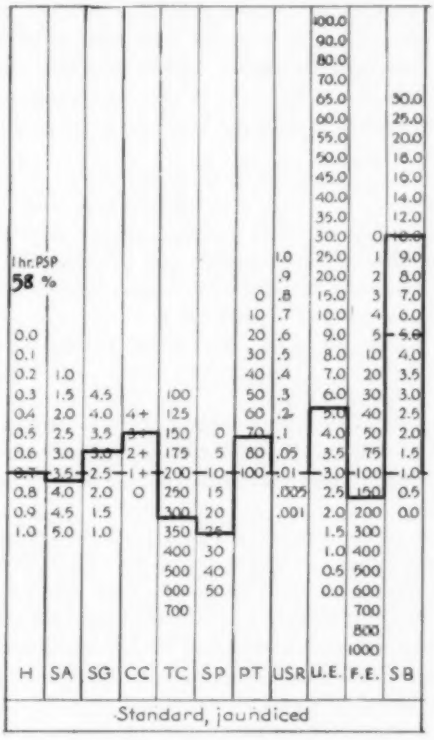


FIG. 11. (*Case 8*) Liver function studies performed April 16 to May 9, 1945, prior to drainage of cystic duct. The urine Ehrlich values shown represent average of three daily determinations. The serum phosphatase value is expressed in Bodansky units in this instance.

chromic in type. Roentgen-ray examinations again revealed the enlarged liver, but no calculi were seen. Esophageal varices were visualized at this time by the roentgenologist, although in 1943 careful study had failed to reveal them. The results of various laboratory studies during this last admission were as shown in figure 11.

The patient was treated by means of bed rest; she received a diet containing carbohydrate 350 grams, protein 150 grams, and fat 88 grams. This is an increase of 38 grams of fat per day over the previously mentioned liver diet and represented an increased allotment of butter and cream. Recent observations have convinced us that the increased palatability of such a diet more than outweighs any possible deleterious effect of the increased fat. In addition to vitamin supplements, both orally and parenterally, the patient received 5 grams of methionine in a liter of 10

per cent glucose as a daily intravenous infusion. No appreciable change in her condition was noted after two weeks. The pruritus was well controlled, however, with 1 mg. of a di-hydroergotamine preparation (DHE–45 *) given by injection every third day. No untoward effects were noted in this or in other patients in whom this product has been used.

Since the remote possibility of a common duct calculus or an inflammatory stricture could not be excluded surgical exploration was requested. On May 8, 1945, Dr. Richard Varco explored the biliary tract; the liver was definitely hobnailed and had the gross appearance of a cirrhosis. The common bile duct was not dilated, no stones were encountered and a probe was readily passed into the duodenum. External biliary drainage was established by means of a catheter inserted into the remaining stump of the cystic duct. A biopsy of the liver was secured.

The patient experienced prompt relief of her pruritus. She was released from the hospital on June 1, 1945, to be followed in the out-patient clinic.

Dr. J. S. McCartney's reports of the histologic findings in the two liver biopsies from this case, are as follows:

1936 (Plate 2c). "This piece of liver tissue shows portions of many lobules. There is a definite increase in connective tissue and new bile duct proliferation in the portal spaces, but no evidence of fatty metamorphosis is seen. The portal cellular infiltrate is largely composed of lymphocytes and plasma cells, the latter being especially prominent." Some of the cholangioles appeared swollen and had atypical epithelium. Conclusion: Early cirrhosis of the liver.

1945 (Plate 2d). "This piece of liver tissue shows portions of many lobules. The lobules vary greatly in size. No central veins are seen. The increase in the portal connective tissue is quite marked with only a minimal amount of new formation of bile ducts and a moderate degree of leukocytic infiltration. The increased portal tissues are quite vascular. In the liver lobules themselves there are fairly numerous bile thrombi which are in part centrally situated and in part at the periphery." Conclusion: Cirrhosis of the liver.

The patient returned to the hospital on July 15, 1944 because of the appearance of hematemesis for the first time. It was learned that four days earlier, following irrigation of the catheter draining the common bile duct, she had developed chills, fever and an increasing jaundice. Vomiting of blood occurred on four occasions on the day of admission. The blood loss was severe and the patient lapsed into a comatose state shortly after admission. Following transfusions of whole blood and infusions of plasma she exhibited a rather remarkable response and regained consciousness. The bleeding recurred, however, and the patient died on July 27, 1944.

At autopsy, the gastrointestinal bleeding was shown to be due to esophageal varices. The liver weighed 3050 grams. The external and cut surfaces were coarsely granular and greenish in color. The common bile duct was patent throughout its course, and was not dilated. The spleen weighed 390 grams and was obviously congested. The remainder of the examination showed nothing of note. Microscopically the sections of the liver revealed marked portal fibrosis with a considerable number of newly formed bile ducts in the portal spaces. The histological picture was essentially the same as that of the biopsy obtained a few months earlier (Plate 2d). Dr. McCartney's conclusion was "advanced cirrhosis of the liver." This was certainly indistinguishable microscopically from an ordinary atrophic or classical Laennec type of cirrhosis, yet it may be emphasized that even after so many years' duration, the liver weighed 3050 gm., and this increase in weight was not due to fat, but rather to connective tissue and new bile ducts, at least in the main.

* Kindly made available to us by Sandoz and Co.

Discussion

The above cases have been selected from our material because they illustrate a number of points regarding prolonged hepatitis which we believe are deserving of more emphasis. The concept of a variety of hepatitis in which the manifestations, at least at some stages of the disease, are wholly or mainly those of regurgitation jaundice, with little or no disturbance of liver cell function, is clearly upheld by our experience. Cases 1 and 6 in the present group are particularly illustrative. In case 6 it was established at operation and by subsequent choledochogram, that there was no extrahepatic biliary tract obstruction, yet the liver was not enlarged, the liver cells appeared normal and the liver cell function prior to operation, as determined by the composite liver function study, was surprisingly normal. The paucity of histologic change in this liver was striking, and this was true, in fact, of others in the group as well. We are not impressed by the tangible gross or microscopic evidence of mechanical biliary obstruction within the liver and since we do not believe that these are cases of choledochitis or extrahepatic obstruction, the exact mechanism of production of regurgitation jaundice remains to be determined. There is rather widespread belief that there is "intrahepatic biliary obstruction" due either to periportal cellular accumulations, to bile thrombi, or to actual increase in size of the liver cords.[5, 6, 31, 32] These factors in varying importance have been believed to serve in a mechanical fashion to obstruct bile flow within the bile capillaries or small bile ducts. When such changes are prominent there is no reason to doubt their rôle in hindering the outflow of bile, but in some cases, at least, neither cellular accumulation, bile thrombi, nor liver cord swelling are at all impressive and one wonders, therefore, whether an entirely different mechanism of regurgitation of bile may not obtain. On the basis of existing evidence, the first possibility here is that of leakage or diapedesis of bile because of increased permeability of the cholangioles * due to injury by the causative agent. This might be thought of as somewhat analogous to the leakage of glomerular filtrate back through the damaged tubules of the kidney in mercury bichloride poisoning, with resultant oliguria and azotemia. Experimental studies have, in fact, indicated that poisons such as toluylenediamine produce jaundice in animals by virtue of causing an increased permeability of the bile capillaries,[34, 35, 36] particularly the ampullae between the capillaries and the primary bile canaliculi, the area designated by Aschoff as the "Achilles heel" of the biliary system.[37] In obstructive jaundice actual rhexis or mechanical rupture of the ampullae has been described.[38] In either event bile is returned to the blood, in the earlier stages at least, mainly via the lymph,[35, 38, 39, 40, 41, 42] and regurgitation jaundice is thus brought about. The idea of regurgitation of bile through injured, although not necessarily broken, biliary radicles was advanced much earlier, however, than the

* This term is used broadly to include the finer biliary radicles, especially the ampullae of the bile capillaries and the primary bile canaliculi in the portal spaces of the liver.

studies of Ohno and his associates,[36] which have just been referred to. Minkowski [43] and Naunyn [44] employed the terms "parapedesis" and "cholangie," respectively, to express the belief that the bile was going the wrong way, i.e., back into the blood, even in cases where there was no definite evidence of biliary obstruction or of cholangitis, although the terms were rather loosely employed, especially "parapedesis" by Minkowski, who evidently related it to regurgitation jaundice generally. The same is true of the term "paracholie" as suggested by Pick.[45] Umber, a pupil of Naunyn's, continued to champion the term "cholangie," [46] and it is significant that he described cases of jaundice to which he applied this term even though evidence of biliary obstruction or of any cholangitic change, was entirely lacking, cases in other words quite similar to those which have just been described. It is quite true that the terms "paracholie" and "cholangie" as employed by Minkowski and Naunyn, respectively, do not insist upon a return to the blood of bile constituents which have actually been within the bile capillaries, but would include a possibility which cannot be excluded with certainty, i.e., that of excretion of these constituents by the liver cells into the lymph spaces of Dissé rather than into the bile capillaries. At the present time there is no basis for a choice between these two possibilities.

Eppinger,[5] and more recently Urteaga [47] have emphasized their belief that bile thrombi are of major significance in the production of jaundice in hepatitis on the basis of actual obstruction of the bile capillaries or canaliculi. While there is no reason to doubt that bile thrombi may be of considerable importance, if present in large enough numbers, we believe that they represent a secondary phenomenon since in some instances, at least, even in the presence of marked regurgitation jaundice, they are not sufficiently numerous to be impressive as the primary factor in the production of jaundice. Their occurrence would fit well, however, with the concept of regurgitation of bile by leakage through damaged bile capillaries or ampullae, since it is logical to assume that in the course of such a "diapedesis" of bile, relatively more water and less solid would leak through into the spaces of Dissé, with the result that whatever bile remained in the capillary would tend to become inspissated, thus favoring the formation of bile thrombi.

The question comes up as to whether in the prolonged cases of hepatitis in which relatively little evidence of reduced hepato-cellular function is observed, there may, nevertheless, have existed at an earlier stage of the disease a considerable liver cell damage and altered function, which by the time the patient is first studied has largely healed leaving nothing but the factor of bile regurgitation. This question has been answered affirmatively by Turner and his associates [18] and by Neefe, Stokes, Reinhold, and Lukens [21a] although in neither instance on the basis of serial histological examinations. The marked increases of urine urobilinogen which are observed in the early stage of epidemic or sporadic hepatitis [62] can only be interpreted as an evidence of hepatocellular damage. Mild increases were observed, later in the disease,

in the majority of the present cases even though other evidence of disturbed liver function was lacking or minimal. Eppinger [5] pointed to the early presence of urobilinogenuria and reduced galactose tolerance, regarding these as evidence of hepatocellular injury. The latter in particular was correlated with evidences of so-called "serous inflammation," other signs of which were: transitory hemoconcentration, widening of Dissé's space and edema of the interacinar spaces. The recent study of Axenfeld and Brass [48] indicates a regular injury of the liver cells particularly in the centers of the lobules, during the first few days of the disease. They also noted evidence of "serous inflammation" such as observed by Eppinger. Proliferation of reticuloendothelial cells and rapid regeneration of liver cells, first by mitosis, later amitosis, was described as occurring regularly. Histologic study of the present liver biopsy material often revealed multinucleated liver cells suggesting regeneration secondary to injury (see Plate 1c, 1d, and 2a) as recently stressed by Lucké.[49] Case 2 in particular illustrates that whatever histologic evidence of liver cell damage exists in these cases may disappear relatively early in the course of the disease, and even while the infectious activity is still marked, as evidenced by the hyperpyrexia at a time when the liver biopsy revealed strikingly little evidence of disease. This type of case suggests that in some instances, at least, a severe functional derangement of the cholangioles and to a lesser extent of the liver cells may be present though not microscopically apparent. In cases 5 and 8 there was a minor evidence of cholangiolar injury, consisting of swollen, atypical epithelium. Case 4 in the present group provides ample evidence that the prolonged, or cholangiolitic type is or can be produced by the same infectious agent responsible for the ordinary, briefer (hepatocellular) variety. Axenfeld and Brass observed various transitions, in cases of epidemic hepatitis, from the initial diffuse hepatocellular injury to the picture of cholangiolitic hepatitis, which they regard simply as the subacute or subchronic stage of the disease.

The prominence of pruritus in the prolonged form of hepatitis deserves further mention. While final proof is lacking that the bile acids or their salts are responsible for pruritus, there can be little question that this symptom is due to a return of some constituent of bile to the blood, and hence that it may be regarded as a very characteristic manifestation of regurgitation jaundice, with relatively normal hepatocellular function. In case 6 of the present series, the occurrence of itching for two months prior to the recognition of jaundice indicates some degree of selectivity in this regurgitation or postulated increase in permeability of the cholangioles, but in this connection it may be emphasized that considerable elevations of serum bilirubin together with mild bilirubinuria may occur without the patient's cognizance. The prompt disappearance of pruritus in cases 5 and 8, following external biliary drainage, is worthy of note. In these instances the bile drainage was considerable, while in case 6 in which it was scanty, the pruritus did not disappear. Here one would have to assume that most of the bile salts being

formed by the liver cell and excreted into the bile were returning promptly to the blood without an enterohepatic circulation, while in cases 5 and 8 the disappearance of itching may well have been due to interruption of the enterohepatic circulation of bile salts.* This would imply, merely, a different degree of injury of the cholangioles in the two cases, in favor of which was the more marked regurgitation jaundice in case 6.

The problem of relationship of hepatitis to cirrhosis of the liver is an exceedingly important one, especially in view of the marked increase in incidence of hepatitis during the war, as discussed at the outset. The majority of investigators favor the view that some cases of hepatitis become chronic in nature and develop diffuse cirrhosis.[5, 6, 12, 13, 48, 50, 51, 64] This is not to be confused with the so-called toxic or postnecrotic cirrhosis, or healed acute yellow atrophy,[52, 53] the occurrence of which has been generally accepted as a sequel of a very severe hepatitis, a relationship especially well documented by Bergstrand.[54] Lucké [55] while accepting the latter type, is not convinced that any relationship exists between epidemic or sporadic hepatitis or so-called catarrhal jaundice on the one hand, and diffuse cirrhosis of the liver on the other. Nevertheless, evidence has been accumulating for a number of years which strongly supports such a relationship. Jones and Minot,[50] in a thorough study of catarrhal jaundice reported in 1923, refer to the development of cirrhosis after several months of jaundice. In speaking of this transition Jones and Minot expressed the following belief: "Serious complications outside of the biliary tract appear to be rare. The term 'complication' has been used in the above discussion in reference to certain untoward occurrences observed in the course of apparently typical cases of infectious jaundice. The advisability of such a term may be questioned by some who may believe that the original diagnosis is at fault. We believe, however, that the above cases warrant the use of the term 'complication.' The first two cases with the infectious cirrhosis occurred in the same family within a week of each other and ran an identical course. The last two cases developed in the midst of well-recognized epidemics, and at the start differed in no way from other cases observed in these epidemics. The final outcome alone differed from the results seen in the other epidemic cases. The serious results reported occurred, we believe, in well authenticated cases of infectious jaundice, were not coincidental, and were probably complications of the original infection."

As Eppinger [6] points out, the usual case of acute hepatitis recovers completely within a few weeks but there are cases in which the jaundice does not disappear, and in which after six months or a year the clinical picture is that of "biliary" cirrhosis, i.e., jaundice, enlarged firm liver, spleen commonly palpable and firm, ascites usually absent. Eppinger would reserve the desig-

* The possibility of eliminating pruritus in cases of longstanding non-obstructive jaundice, by partial interference with the enterohepatic circulation, was suggested to us by Dr. Richard Varco.

nation biliary cirrhosis for those cases in which so-called "catarrhal" jaundice persists and gradually exhibits more and more of the features of cirrhosis. From a clinical standpoint this form of cirrhosis is most compatible with that originally described by Hanot.[56] According to Karsner [53] Hanot's cirrhosis is probably comprised by the conditions described by Lichtman,[6] Klemperer [57] and Rössle,[58] under the following designations, and, according to Karsner, the following histologic differences:

Lichtman: Non-obstructive cholangitic biliary cirrhosis Klemperer: Chronic intrahepatic obliterating cholangitis	Evidence of cholangitis and fibrosis in portal spaces.
Rössle: Cholangiolitic or cholangiotoxic cirrhosis	Intralobular fibrosis and cellular infiltration.

Karsner [53] mentions an example of the latter variety which he studied. This was in a male, 32, a periodic alcoholic, who had had repeated attacks of what appeared to be acute hepatitis over the course of 10 years. There were jaundice, enlargement of the spleen and liver but no ascites, in other words a clinical picture corresponding with Hanot's cirrhosis. At autopsy the liver weighed 4100 gm. and exhibited "cholangiolitic biliary" cirrhosis. If one can judge from the microphotographs in Karsner's paper, this was not a fatty cirrhosis. It may be noted again, with respect to the question of repeated attacks of hepatitis, that these are well known and that one attack does not necessarily confer immunity. The question is whether in such instances one is dealing with a continuous chronic virus infection having latent periods and exacerbations, whether a re-infection has occurred, or whether, after the subsidence of the virus infection, the progression of the disease is due to inability of the once damaged liver to inactivate or detoxify some injurious substance, possibly of metabolic origin. In case 8 of the present series, certainly the most remarkable insofar as the question of transition of infectious hepatitis to cirrhosis is concerned, the history indicated a continuous chronic disease of 34 years' duration following the initial acute episode. As a striking instance of individual variation it may be noted again that the sister, who had also suffered from infectious jaundice 34 years previously, recovered completely and has had no further jaundice nor manifestations of liver disease. Bloomfield [51] was particularly impressed with the concept of a latent chronic form of hepatitis gradually progressing to a clinically manifest cirrhosis of the liver, and cited numerous cases apparently exhibiting such transitions. Steigmann and Popper [31] likewise regard chronic hepatitis and cirrhosis as identical and describe two cases of unusually prolonged acute hepatitis in which laparotomy with biopsy revealed clear cut evidence of developing cirrhosis. The histologic changes described agree well with the concept of a cholangiolitic cirrhosis which is perhaps the best term to designate briefly the type of cirrhosis developing after hepatitis. Axenfeld and Brass, in an extensive study of epidemic and sporadic hepatitis carried out with the aid of liver biopsy and reported in 1942,[48] conclude that cholangiolitic hepatitis

represents a subacute or sub-chronic stage of the disease, and that in some instances definite transition to cirrhosis of the liver is observed.

Bloomfield's cases, in the main, were instances of ordinary portal cirrhosis and the majority were in alcoholics, only 10 per cent giving a history of a previous episode of jaundice. In Patek's study of cirrhosis [59] the incidence of a previous episode of jaundice was but 5 per cent, in other words approximately that of the population at large. Most of Patek's cases, like Bloomfield's, were chronic alcoholics, so that it may be assumed that a fatty liver and hence an intermediate fatty cirrhosis was the usual sequence of events in the development of the portal or atrophic cirrhosis which was observed. It must be emphasized that there are probably at least two mechanisms by which a so-called hypertrophic cirrhosis may gradually become atrophic: (1) The large fatty cirrhosis which loses fat and gains scar tissue, with concomitant shrinking. (2) The large relatively non-fatty cholangiolitic cirrhosis in which, initially, there are periportal lymphocytic foci, bile thrombi, bile duct proliferation, hyperplasia of reticular cells, and beginning fibrosis; later extensive fibrosis with resultant hardening and shrinking. Lichtman [6] records an excellent example of the latter type. Fatty cirrhosis is regarded as probably not related to hepatitis, but rather to chronic dietary deficiency often on the basis of alcoholism; the non-fatty, cholangiolitic cirrhosis is believed, at least in many instances, to be the sequel to infectious hepatitis. It is regarded as very doubtful that the end stages of the two diseases can always be distinguished with certainty on anatomic or histologic grounds. This is intended to imply, simply, that what may first present as "hypertrophic" biliary, or Hanot type of cirrhosis may eventuate in an ordinary portal or atrophic cirrhosis. It is believed that the distinction of fatty or dietary cirrhosis from the non-fatty or cholangiolitic type may well have therapeutic implications at least in the earlier stages since there is every reason to believe that cholin-cystin or methionine, or a high protein diet would be more effective in the former than in the latter type.

It is not meant to imply that a cirrhosis secondary to hepatitis might not become fatty if the individual, because of anorexia, were on a deficient diet for a sufficiently long period. Conversely there is little doubt that by the use of lipotropic substances, much of the fat in an alcoholic or dietary cirrhosis may be mobilized with resultant shrinking of the liver. It is also not implied that fat, per se, causes cirrhosis of the liver, but only that a fatty liver represents the early stage of evolution of so-called alcoholic or dietary cirrhosis. in contradistinction to the non-fatty cholangiolitic hepatitis which is believed to represent the early stage in development of cholangiolitic cirrhosis.

In the foregoing we have emphasized the question of relationship between hepatitis and "biliary" cirrhosis because our own material lends support to such a concept. Cases 5, 7, and 8 have been selected as especially illustrative. In case 5 the manner of onset of the disease was indistinguishable from that of ordinary sporadic or epidemic hepatitis, although a history of definite

contact was not established. The improvement during the first hospital admission, with subsequent relapse, when correlated with the progression from hepatitis without cirrhosis (Plate 2a) to hepatitis with cirrhosis (Plate 2b), form a rather convincing picture of the development of cirrhosis in a case of prolonged hepatitis. We believe that case 7 likewise exemplifies this transition. Whether the initial hepatitis in either instance was identical with epidemic hepatitis is not known. The fully developed clinical picture in both of these cases was characterized by pruritus, regurgitation jaundice without ascites, enlarged liver and spleen, hypercholesterolemia and hyperphosphatasemia. This syndrome is suggestive of xanthomatous biliary cirrhosis, and in this connection we would emphasize, in agreement with Parkes-Weber,[57] that the entire clinical picture of this latter condition may be produced by, or exist in association with, a cirrhosis in which no xanthomata of the extra- or intrahepatic bile ducts are to be found at autopsy. A case of this type has recently been described by us.[61] The question may be raised as to whether such instances are not late stages of a chronic cholangiolitic hepatitis with progressive cirrhosis. As Hanger and Gutman [32] have shown, entirely similar chemical findings may be observed in the cholangiolitic hepatitis seen at times following arsphenamine therapy, so that there is little need of ascribing a marked hypercholesterolemia and hyperphosphatasemia to a metabolic error. One may well ask, on the contrary, whether certain forms of hepatitis and cirrhosis do not actually give impetus to an overproduction of these substances.

In the foregoing, we have emphasized the cholangiolitic type of hepatitis and its transition to a similar variety of cirrhosis. We do not mean to imply, however, that this is the only variety of transition, and in fact, we have seen a number of other instances in which cirrhosis followed infectious hepatitis, but in which the regurgitation jaundice of the cholangiolitic type, with its characteristic prints, hypercholesterolemia, and hyperphosphatasemia, was not present.

Summary and Conclusions

1. Certain cases of prolonged hepatitis exhibit normal or relatively normal hepatocellular function in the presence of marked regurgitation jaundice. The histologic changes often appear inadequate to account for the jaundice. These consist in the main of a varying amount of periportal lymphocytic infiltration, bilirubin staining of the liver cells especially in the centers of the lobules, and bile thrombi in variable number. In the absence of sufficient evidence of this type to indicate intrahepatic biliary obstruction, it is believed that the continued regurgitation of bile supports the concept of increased permeability (functional injury) of the cholangioles. This regurgitation is manifested by a prompt direct (1′) hyperbilirubinemia, hypercholesterolemia, hyperphosphatasemia, and pruritus.

2. In some cases of epidemic hepatitis liver biopsy may fail to reveal

histologic evidence of any appreciable hepatocellular injury at a relatively early period of the disease, when infectious activity is still manifest. Since, in these cases, there is often some residual evidence of reduced hepatocellular function, it is believed that there was, initially, a more marked liver cell injury, and that the prolonged regurgitation jaundice simply indicates a more severe affection of the intrahepatic bile duct system than in the ordinary case.

3. The problem of the relation of prolonged or cholangiolitic hepatitis to the development of cirrhosis is considered; further examples representing transition from hepatitis to cirrhosis are discussed and the term cholangiolitic cirrhosis is suggested as being more appropriate and distinctive than "hypertrophic biliary cirrhosis." The prominence of regurgitation jaundice without ascites, but with pruritus, hypercholesterolemia and hyperphosphatasemia in this group of cases, is emphasized. The end stages of the cholangiolitic cirrhosis following prolonged hepatitis may be indistinguishable, anatomically, from ordinary atrophic or portal cirrhosis. The cholangiolitic type of hypertrophic cirrhosis is believed, however, to be distinct from the "hypertrophic" fatty cirrhosis which represents an intermediate stage between the fatty liver and the atrophic cirrhosis of chronic alcoholics or other conditions in which dietary deficiency is probably the most important etiologic factor.

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MEDICINE AND EDUCATION *

By Ernest E. Irons, F.A.C.P., *Chicago, Illinois*

Education has been described as the "taking on of the arts and sciences and of moral attitudes which make up the fabric of civilization." In this process, educated people acquire an appreciation of values, the ability to think and to see the relations of the values to each other in human living. Unfortunately, as George Vincent put it, many people do not think; they merely rearrange their prejudices. The Harvard report well states the general problem. "The aim of education should be to prepare an individual to become an expert both in some particular vocation or art and in the general art of the free man and citizen. Thus the two kinds of education once given separately to different social classes must be given to all alike." "The aim of general education may be defined as that of providing the broad critical sense by which to recognize competence in any field." The observation of Henry Morrison that "We do not learn what to do, but rather become the kind of people who will know what to do," is well exemplified in the varying quality of performance of interns in our hospitals.

In medicine defects in education become evident, when we analyze the quality and performance of the graduates of medical schools. I speak now of the mentally well endowed students, ambitious, hard working, who nevertheless fail to prosper as well as they might, because of an evident lack of training to think, and to set down their thoughts in good English. This inferiority, or perhaps one should say more politely, this lack of completeness in premedical education in a number of respects that go to make up the somewhat nebulous term "culture," has been accentuated by the recent acceleration of medical education made necessary by the needs of the armed services. But it had been increasingly evident in the decades preceding the present war.

War is always wasteful and its serious effects on education in general are clearly evident in the field of medicine. Besides the distraction and disturbance of general thinking, medicine has suffered through the abbreviation of premedical preparation, the acceleration of the medical course with its condensation of four years into three; the concentration of the internship, and the elimination of residencies for two thirds of the young physicians under the formula that allotted nine months each to internship, assistant residency and residency. To those of us who were brought face to face with the medical emergency of the armed forces, the acceleration of the medical educational program seemed a necessary and therefore a desirable compromise, to which we subscribed as a wartime measure. This acquiescence, in keeping with the evident needs of the hour, did not mean that we were unaware that educational standards were being sacrificed to immediate necessity by these pro-

* Presidential Address, Victory Convocation, Twenty-Seventh Annual Session, American College of Physicians, Philadelphia, May 15, 1946.

cedures. The speeding up of the curriculum with shortening of some courses and the introduction of others, no doubt eliminated some time-honored, but unnecessary courses, which up to then, entrenched behind ramparts of custom and personal interest, had withstood previous efforts to remove them. But against this relatively slight gain must be assessed the hurry and tendency to superficiality of a rapidly moving program, and the impossibility of exploring adequately the by-paths of educational interest. In his hurried acquisition of prescribed facts, the student lacked the time as well as the strength for collateral reading; his jaded mind failed to respond to such impulses of curiosity as he might fortunately experience. The superior students felt this keenly; the weaker students never knew what they missed.

Later in the war program, those in military authority were given unfortunate advice regarding education which led to the reduction of the supply of properly trained candidates for medical schools. The serious results of this mistaken policy will be felt by the public for years to come. Nursing education has suffered in much the same way as has medical education.

Perhaps a physician is presumptuous in discussing problems of general education in regard to which professional educators are vigorously battling among themselves, seemingly unable to agree. Nevertheless, most of the faults that educators of the several camps point out, are clearly evident in results of our attempted education of physicians. We lament the lessening knowledge of the classics, the limitation of sources of knowledge by lack of even superficial facility not only in Greek and Latin, but in modern languages such as French, German and Spanish.

The tremendous advances in science in this country have indeed overshadowed the influence of the classics. But this imbalance exists throughout general education also, and is attributable to the expansion of the educational system, changes in society, and to what has been described as the "headlong growth of knowledge." Classicism flourished when but little was being done to remedy the ills of poverty and low standards of living. Then came science and mechanical arts which raised standards of living so that the deficiencies of previous centuries under classicism became evident. Today, neither classicism nor science can march alone.

In medicine the balance can be restored in part at least by the assumption of an increased leisure, or perhaps better a deliberateness and thoroughness which will decrease the unreasonably rapid tempo of preparation for medical and scientific education. By insistence on a more thorough ground work in the classics, languages and history, the student will acquire tools and a cultural point of view that will serve him well as a responsible citizen in a democracy and in his educational life which has only begun when he leaves the portals of college and medical school. The cultural background should be broad, and the tools of good quality.

Not all people, even some of the intelligent, are interested in the thought-mechanisms of the ancients, as presented in the 100 books recommended by some educational leaders as necessary to education. But there is much sound

advice, as well as a certain pathos in the voices of the classicists, small in number but vociferous, crying aloud in a wilderness of science.

Before accepting at face value the charges of one group of educators that an opposing group is "authoritarian" or that another is "practical" or "vocational" and therefore lacks intellectual ideals, it might be profitable, even at the risk of seeming repetitive and perhaps "undemocratic," to consider the purposes to which the recipients of education plan to devote what they learn. For, unpleasant as it may be to those who would insist that we are born "free and equal," the fact remains that we vary greatly in our mental and physical endowments as well as in our acquired ambitions. Not all people in like positions are of like productive ability. Some, more than others, are able from the beginning to assimilate cultural elements; some seem incapable of being educated.

In medicine there is an ever increasing need for scholarly attainment not alone in the scientific fields so that the physician may understand the language and utilize the discoveries of the lightning-like advances of science, but in cultural and historical fields so that he may evaluate properly the medical, social and political changes about him. He should begin as early as possible to prepare himself for intellectual leadership.

But in medicine and I suspect in other educational groups the difficulty goes even deeper. Many candidates for admission to medical schools lack facility in reading, writing and spelling and consequently in ability to acquire and express ideas. They do not know the rudiments of English grammar. This in turn reverts to slovenly training in the secondary grades. One wonders how many of their teachers know the fundamentals of English grammar. And in those schools of supposedly better heritage in which education is called progressive, the slogan of making education pleasant and non-competitive negatives in practice the acquirement of precise knowledge and exact attainment. The contention that "usage" should be the supreme guide to the acquirement of good English overlooks the fact that usage is concerned with the choice of words to express ideas and cannot replace correct spelling and grammar, which are based on formal conventions. Possibly while the youngster is being taught to think, he might be induced to learn to add, subtract and spell.

The apparent deterioration in quality of modern secondary education, while perhaps due in part to unwise emphasis on the joy of making education pleasant for the child, is not to be charged to sabotage of standards, or perverseness, or original sin. Gideonse has emphasized what has been repeatedly pointed out, that a chief cause of educational ineffectiveness is related to the rapid extension of education downward. It is a defect not peculiarly American, but according to reports is a recognized problem in English, Dutch, French and Russian education. This expansion of education downward to large masses of people previously scarcely educated at all, necessarily involves dilution of effort, and makes necessary the inclusion in the teaching group of a number who themselves are not up to previous stand-

ards. Reduction of standards of quality of goods or of services results in reduction of standards of living, in this case reduction in standards of education. This is especially true in large cities, many of whose school systems obviously have outgrown their physical facilities, and perhaps less evidently, but just as fatally, their teaching force. In rural communities the problem presents what the Director of Education, Mr. Studebaker, has called the "inefficiency of smallness." This is being remedied by the establishment of regional and township high schools. The little red school house still serves well, but its scope is limited, and needs to be supplemented by a larger and more advanced unit.

The repair of defects in secondary and general education will require time and vast effort. Even after entrance to the decelerated medical course, students as now educated may be introduced to collateral lines of reading, such as medical history, which itself inevitably will necessitate some exposure to political and economic history. The correction of other fundamental faults in the preparation for the medical as well as for other professions awaits also the elimination of the frequently wasted two years in the primary grades and the replacement of mere college credits by real educational values. Such a general education should provide a broad cultural basis in the humanities as well as in science, a change which will afford untold satisfactions in later life.

Within the structure of the medical curriculum itself, there have developed over the years stresses and strains between preclinical and clinical departments, again largely ascribable to the rapid increase in knowledge, which has forced specialization in the basic and preclinical medical subjects, just as in the clinical. There have resulted educational fissures and gaps; sometimes major quakes have further separated basic from clinical medicine. These faults are being slowly eliminated through the attainment of a better understanding of the problems of each group by the other.

It may be urged that the physician is now 26 or 27 years old when he enters the practice of medicine, that his preliminary and medical education has already been improved by the creation of the combined college-medical course of six or seven years, that the need for physicians demands an increase rather than a decrease in output, and that increased training adds indirectly to the cost of medical care. All this is admitted. But relative economic and educational values need to be considered. Some years ago when the evident educational deficiencies of medicine were beginning to be remedied, a proposal was suddenly made to reduce standards of medical education, so that there would be more doctors available to go to understaffed and neglected areas especially in the South. This proposal, by men sincere, but of limited vision, failed to consider that the medical plight of these areas was only symptomatic of bad fundamental economic conditions, that reduced standards of training would reduce quality of performance, and that men willing to accept such inferior training would lack also the idealism necessary to sustain them in situations of increased difficulty. Fortunately the economic origin

of this distress was recognized before the destruction of standards of medical education had been accomplished.

Some 10 years ago the Commonwealth Fund undertook to provide education for men in medicine under an agreement that they would settle in backward and poorly staffed communities. In practice it was found, however, that many of these men tended to avoid the very districts where they were most needed and that some failed to keep the agreement at all. Without condoning the breaking of agreements it may be observed that in the absence of suitable economic and hospital facilities one could hardly expect progressive young doctors to resign themselves to making bricks without straw. In spite of chimerical arguments of recent years that somehow economic laws have changed, the laws of supply and demand, of human nature, and of opportunity, remain the same as in previous centuries in education as in business.

Education and Medical Research

The bounding progress of scientific knowledge, to which medicine owes much of its own astonishing accomplishments in the amelioration of suffering and the saving of lives, has come through the free mental activity of men trained to think rationally and at the same time to give free rein to their imaginations. While entirely new concepts occasionally necessitate an extensive rearrangement of previously held notions, in the main the progress of today rests on the labor of yesterday.

The man who proposes to engage in research requires first a broad general education in order that he may develop an unconscious critical sense, the first line of defense against wild and unworkable theories. Some men never acquire this discriminative ability nor have they the diligence to learn what has already been done, and they fall victims to, and sometimes become protagonists of procedures which in the end do harm to the cause of medical science. Some even deserve the cynical comment of a celebrated wit: "If you steal from one author, it's plagiarism; if you steal from many, it's research." Manifestly this remark is unfair to good research. It does, however, characterize certain reports which masquerade under the name of research. Inquiry usually will disclose gaps in the early education of such authors.

The benefits of fundamental research, the result of private expenditure of some thousands of dollars, have been so overwhelmingly demonstrated in the war now ending, that research is confronted with a new problem, that of withstanding popularity. It is assumed that since the value of research to the nation has been so outstanding, more research will be still better and the government should invest millions against the previous privately supplied thousands, and go in for the purchase of research in a big way. Varying opinions are held as to the advisability of government subsidized research; some hold that government funds are needed to reinforce private sources now being exhausted by heavy tax burdens; others maintain that the entry

of government funds into the research field will itself discourage the further contribution of private sources.

But more important than these questions is that of the method of utilization of these funds. Imagination and ideas cannot be grown to order; they come from unsuspected places. After the initial idea or concept is born, collateral lines of approach must be explored patiently and often without tangible result. The scientific method cannot be forced. And so research must be free—free from the demands of today or tomorrow. Such freedom is best realized in universities; workers must be under no compulsion other than the inner driving force of their genius. If government funds are to be used to advantage, they should be under the direction of universities which have already demonstrated their ability to utilize to advantage their own funds free from any governmental obligation or political interference.

Education in Relation to Statistics and Propaganda

Physicians share with other citizens the necessity of education in the interpretation of statistics. It is easy to state only a part of the truth. Recently the statement appeared, quoting from an authoritative article on nutrition: "Only one American in a thousand is really well fed." One is led to conclude that Americans as a whole are existing on a marginal diet. The complete sentence reads "Only one American in a thousand is really well fed, in the sense that no further improvement in his physical condition could be made by changes in his diet." While one might challenge the general application of this latter statement, it is clear that the use alone of the first portion of the sentence is an attempt to influence public opinion by disseminating an untruth.

It is claimed that an alarming percentage of school children fail to meet ideal figures of height or weight. Should a couple of pounds over or under the average standard or a cavity in one tooth consign an otherwise healthy child to the category of an imperfect and therefore defective class?

The same kind of misinterpretations of draft statistics has given the impression to the uninformed that the American nation physically is about to fall to pieces. We have been told that the 4,000,000 rejections of draftees indicate a frightful state of medical decrepitude, which requires an immediate rearrangement of all medical service. The facts are that only a fraction of these rejections were for remediable medical defects. By a sane program many defects can no doubt be prevented or remedied, but illiteracy and feeblemindedness can hardly be cured by any system of medicine. The fallacies involved in assuming that the 4,000,000 draft rejections are a fair index of the nation's health are further emphasized by the recent willingness of the army, which even now must have able bodied men, to enlist thousands of these same men who were previously rejected.

Still other misquotations and misuse of statistics are made in discussions of statistics of morbidity and mortality. League of Nations' statistics are

used without discrimination as to conditions existing in countries under discussion. The manufacture of misleading data out of incompletely digested statistics seems to be a too common practice in some governmental circles.

In this country in support of a highly desirable nationwide campaign against venereal disease, figures on the incidence of syphilis among poor negro populations in backward counties in the South were quoted as if the same conditions were present in the north central states. The excuse given was that people must be shocked into action.

Special Boards

The widening scope of medical knowledge, in addition to requiring vastly more information and preparation of the modern doctor, has made it necessary for some to devote still more time and effort in perfecting themselves in special departments; therefore special fields developed and more recently special examining boards to determine minimal standards of performance in these specialties. The operation of the several boards of medical specialties designed primarily for the protection of the public, has resulted in an amazing and unanticipated stimulation of thousands of young doctors to spend at least five additional years in preparation in their chosen specialties. Whether or not they finally pass the boards, the quality of their current and subsequent service to the public is greatly enhanced, and a further improvement of medical public service results. A broad educational foundation will assist the young physician to appraise the value in medical practice of the many new methods and instruments designed to contribute to accuracy and completeness of diagnosis. Some of these, like some drugs, will be found valuable; others will be determined inaccurate or misleading. The acquirement of clinical sense and experience will help the physician to use such apparatus intelligently where needed, and to avoid their use as occupational gadgets.

The special boards, unlike boards of state licensure, have no legal status, and the participation of any doctor is entirely voluntary. The wide acceptance of standards set by special boards often has led organizations and hospitals charged with the selection of staffs to require certification by a special board as a prerequisite for appointment. With such appointments, the boards have nothing to do; they have only set certain standards, for certification, of which any organization may avail itself. No doubt there are many men of equal ability and experience who have not cared to apply for certification or submit to examination. The educational requirements preliminary to admission to examination are suggested by the boards for the protection of the candidates, so that they shall not spend five or more years in inferior training only to find later when the golden period of opportunity of youth has passed, that they have failed. Here, too, it is tragic to observe the occasional young doctor who comes for his examination before special boards with a reasonable preparation of theory and factual information, full

of ambition, idealism and often imagination, but hampered by an evidently faulty secondary and premedical education and unable adequately to express his ideas in intelligible and decipherable English.

Some concern has been expressed over the great increase in physicians who are taking board examinations because it is feared that soon there may be too many specialists. Here again, it would seem that we may safely depend on the law of supply and demand. Certainly the desire to acquire additional preparation and facility in a branch of medicine is to be encouraged, rather than condemned; the public will gain in better quality of service. There is, however, complaint from many patients, that the young doctor having passed his board, now feels that he is relieved of all obligation to care for his patients in their homes when they are unable to come to him. While the younger physician must conserve his time and strength if he is to continue to grow in medicine, he should not forget that the greatest gratification in the practice of medicine is the close patient-physician relationship of the family doctor. He will do well not to allow a false estimate of his own dignity, nor too much solicitude for his own convenience, or for financial gain, to rob him of this jewel among the rewards of medicine. He should not assume that by improving his qualifications for the practice of medicine, he has disqualified himself as family advisor and friend. His experience will be greatly enriched by his observation of even minor illnesses in the home. The better prepared physician of the future will still retain the ideals of medicine; the family doctor will not have passed—he will have improved.

Medical problems of the future, including prosecution of medical research foretoken the necessity of even more educational preparation than is needed to meet the problems of our day. Some familiarity with the events and thinking of the past will help the physician to understand the significance of current social, economic and political changes. A knowledge of history will contribute to tolerance, and at the same time will tend to prevent errors of judgment incident to emotional thinking. A good general education is necessary to the physician of the future, so that with its aid, he may excel in his profession, and still more important, he may take a worthy place in the citizenship of a democracy in a free society.

INFECTIOUS MONONUCLEOSIS: REPORT OF AN EPIDEMIC IN AN ARMY POST.*
Part II

By Harry F. Wechsler, Lt. Col., Arthur H. Rosenblum, Capt., and Charles T. Sills, Capt.

11. The Cardiovascular System. Our knowledge of the possible effects of infectious mononucleosis on the heart is extremely meager. The literature on this subject is summarized, but not critically analyzed, by Bernstein.[10] He, however, states that "despite the scantiness of these bits of evidence, one wonders whether certain of the so-called rheumatic hearts encountered in individuals with no history of rheumatic fever or its equivalents, may not date back to a seizure of infectious mononucleosis."

In 1914, two English physicians, Pruen [50] and Kirkland,[51] under the title of "Epidemic Cervical Adenitis with Cardiac Complications," reported their observations on a large number of cases which they had seen in 1912. The former observer had 14 cases with cardiac complications out of a total of 60, while the latter had 10 per cent of myocardial or endocardial involvement in several hundred cases. The disease they describe has little resemblance to infectious mononucleosis and no blood counts were taken. Indeed, the authors themselves did not believe they were dealing with infectious mononucleosis but with a streptococcus infection. Smears of the throats showed streptococci and blood culture in several cases grew the same organism.

Longcope,[35] in 1922, reported 10 cases of infectious mononucleosis, two of whom had premature contractions. The first case, a woman of 30, can be dismissed, as no further observations were made. The second, however, is more interesting. An Italian girl of 12, following a tonsillectomy 19 days before admission, had intermittent fever, malaise, constipation and occasional vomiting. Five days before admission, she developed a red, macular, generalized rash and abdominal pains, which were at times confined to the right side. She had had frequent attacks of tonsillitis previously, and six months before admission she had had pains in the right shoulder without fever for one month. Physical examination showed a macular rash on the abdomen, slight injection of the throat, enlarged submaxillary, axillary and inguinal nodes, small but tender posterior cervical nodes, a soft systolic murmur at the apex, some accentuation of the pulmonic second sound and premature contractions. The blood count was characteristic of infectious mononucleosis with the exception of the red blood cell count. In the space of three days, there was a drop in the red count from 7,140,000 to 3,800,000

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and in the hemoglobin from 80 per cent to 68 per cent. Such a drop does not occur in infectious mononucleosis without the presence of a complication and one must, therefore, either doubt the correctness of the diagnosis or conclude that the infectious mononucleosis was complicating some other illness such as rheumatic fever. An electrocardiogram is reported in this case as showing a P–R interval of 0.14 to 0.16 sec., ventricular premature contractions and an inverted T-wave. As no lead is mentioned, the significance of the inverted T-wave must remain in doubt.

In 1930 Du Bois [52] reported the case of a 26 year old male with infectious mononucleosis who developed an extensive empyema of the right pleural cavity. At autopsy, a rheumatic-like vegetation was found on the mitral valve. Although the pleural fluid was said to be sterile, it is highly probable that the empyema was due to a secondary infection and could also have been the cause of the endocarditis.

Finally, Bradshaw,[53] in 1931, reported the case of a young girl of 17, who was known to have had a normal heart previously and who, as rapidly as six weeks after the recovery from an attack of infectious mononucleosis, was found to have definite evidence of mitral stenosis. The clinical description and the blood counts could very well fit a case of infectious mononucleosis with jaundice, except that the author states that only rarely was a morphologically abnormal lymphocyte found. The rapidity with which evidence of mitral stenosis was discovered after her illness and the persistence and rapid progression of the lesion would favor the view that the murmur had been present prior to her attack of infectious mononucleosis rather than secondary to an acute valvulitis. It is well known that the murmur of mitral stenosis is frequently difficult to hear or is even inaudible at times.

Our attention was directed to the heart in infectious mononucleosis by the unexpected discovery of a markedly prolonged P–R interval in an otherwise typical case. This case will be described in detail.

Case Report

A negro soldier, aged 29, was admitted on September 7, 1943, with the complaints of sore throat, chills, fever, headache, nausea, vomiting and pains in the epigastrium. These symptoms began abruptly the day previously. He had malaria in 1933, with no recurrence since. In 1941, he was treated for "low blood pressure" because of dizziness. He had been admitted to this hospital on May 17, 1943, for a non-specific urethral discharge. During his stay, he complained of epigastric pains, bloating and belching. A gastrointestinal series and gall-bladder roentgen-rays were negative. A gastric analysis revealed a low acidity. He was discharged to duty on July 2, 1943.

On admission, his temperature was 103° F. and his pulse rate 94. Physical examination revealed a well-developed and well-nourished male adult, who looked acutely ill. The pharynx and tonsils were injected. There was a moderate generalized lymphadenopathy. The spleen was palpable one finger's-breadth below the costal arch. The rest of the examination was essentially negative.

The blood count on admission was: white blood cells 10,700; neutrophiles 89 per cent, lymphocytes 10, eosinophiles 1. Serial blood counts revealed a progressive decrease in his total white blood cell count and a rising mononucleosis. Large num-

bers of "leukocytoid" lymphocytes were present. The white blood cell count on October 6, 1943 was: white blood cells 5,900; neutrophiles 33, lymphocytes 67. The heterophile antibody agglutination titer on September 10 was 1:56 and on October 6, 1:448.

He had a fever for but two days and remained afebrile thereafter. On September 11, four days after admission, he complained of sharp precordial pains. Because of a heart rate of 44 and a marked sinus arrhythmia, an electrocardiogram was taken. It showed a P–R interval of 0.24 sec. and a rate of 40.

He continued to complain of occasional precordial pains. The bradycardia persisted. A faint soft systolic murmur was audible over the apex. Serial electrocardiograms (figure 6) showed an increasing degree of heart block. On November 6, the P–R interval was 0.44 sec. In December and the early part of January (figure 7), a second degree heart block was present, usually with a 7:4 ratio. Thereafter, the P–R interval varied between 0.36 sec. and 0.42 sec.

The erythrocyte sedimentation rate, which was 29 mm. in one hour on admission, rose to 56 mm. a week later and then remained within normal limits, except for a reading of 25 mm. on November 22 and of 35 mm. on December 3. The blood Kahn test was negative. No sickling was present. Bacterial agglutination titers were: *E. typhosa* 1:80; Para A and B, negative; *B. abortus*, negative; Proteus OX–19, negative. Throat cultures for *Streptococcus hemolyticus* were negative. An anti-fibrinolysin titer, performed four months after the onset of his illness was 2 plus and then gradually became negative. Roentgen-rays of the chest showed a moderate increase in the size of his heart by November.

After the first few weeks he had no complaints. A diastolic murmur was never audible. The bradycardia, systolic murmur, moderate enlargement of the cardiac shadow and a normal sedimentation rate were present on his discharge, eight months after the onset of his illness.

Because of this striking and unusual case, electrocardiograms were taken of 223 patients in this series. Excluding deviations of the S–T segments, low voltage and minor slurring of the QRS complexes, 53 patients had abnormal electrocardiograms, 23 per cent of the group. These patients were closely observed, and the analysis of our findings is summarized.

Previous History: There were six patients with a past history suggestive of rheumatic fever. Three of these had suffered from a definite polyarthritis, one had scarlet fever at the age of five and pains in the knees at the age of 13, one had vague rheumatic pains in the legs between the ages of seven and 12, and the last had an attack of swelling and weakness of the right knee, unaccompanied by fever, four or five years prior to admission. One patient, without a history of rheumatic fever, had been found to have a heart murmur three years previously.

Clinical Course: In general, there was little to differentiate this group from those with normal electrocardiograms. Those patients with acute onset and febrile course were more severely ill, and their temperatures tended to reach a higher peak. There were 49 per cent of this group with temperatures of 102° F. and over, as against 32 per cent for the series as a whole. On the other hand, there were 13 cases who were afebrile during their hospital stay. There was a greater tendency toward relapses of the infectious mononucleosis, eight of the group suffering such a relapse. There were no cardiac symptoms, except for an occasional patient who complained of inter-

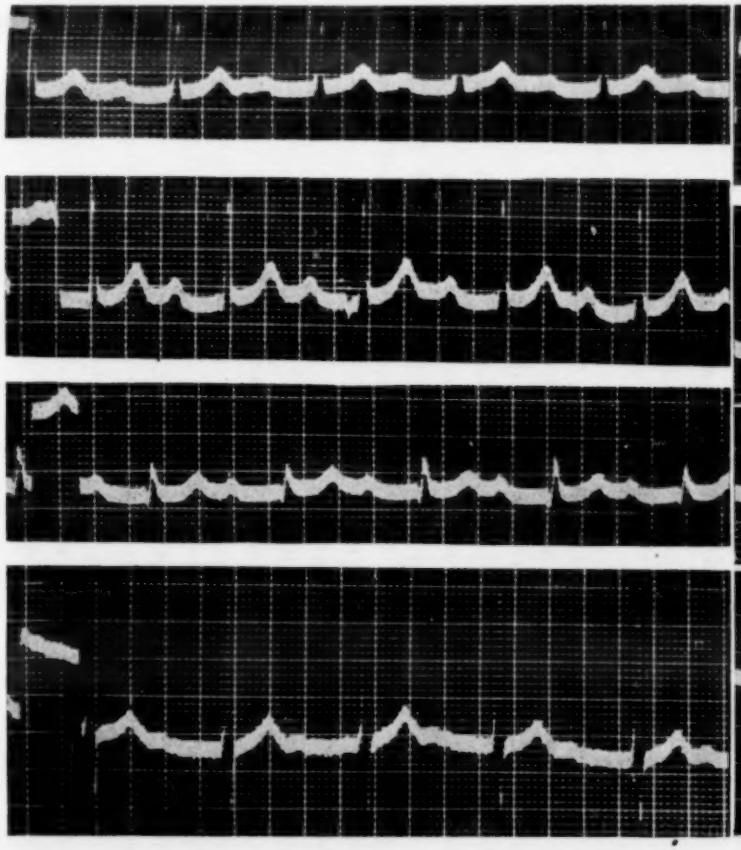


Fig. 6.

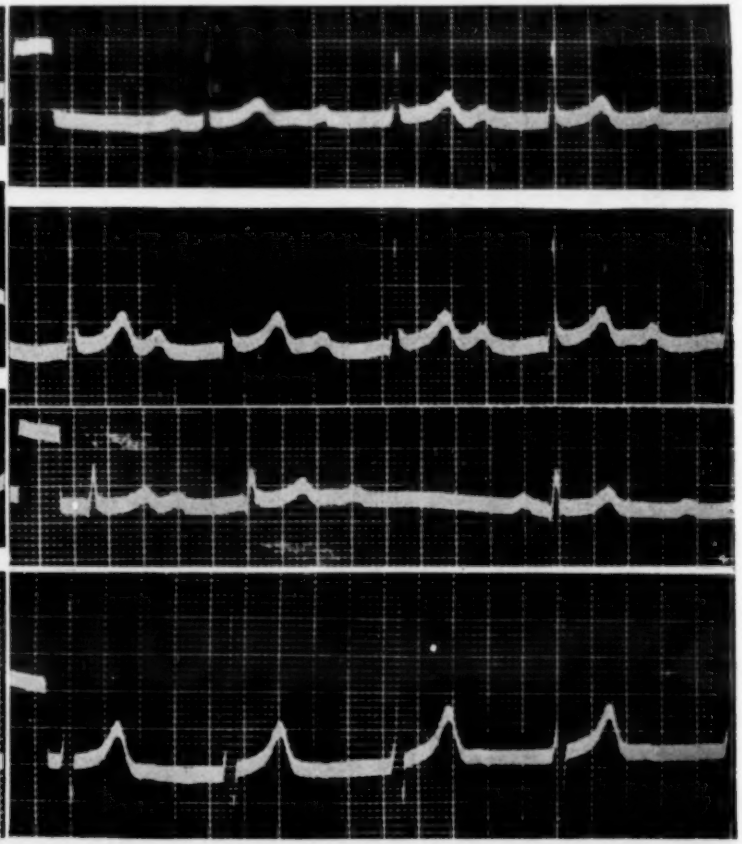


Fig. 7.

Fig. 6. Electrocardiogram taken Oct. 11, 1943. The rate is 75 and the P–R interval 0.32 sec. There is a blocked auricular premature systole in Lead II.

Fig. 7. Electrocardiogram taken Jan. 3, 1944. The rate is 60 and the P–R interval 0.40 sec. A ventricular complex is dropped in Lead III and is followed by a complex with a normal P–R interval.

mittent sharp precordial pains. The other manifestations of the disease were as varied as for the series as a whole. There were two patients with pneumonia, one of whom showed a polymorphous type of eruption in addition. Six others of the group had eruptions, three scarlatiniform, two morbilliform and one maculopapular. There were two patients with jaundice and one with nephritis.

Cardiac Findings: Abnormal physical findings relative to the heart were scanty. Cardiac enlargement was demonstrable in only three of the cases. In one there was a history of a "murmur discovered three years previously." A presystolic murmur was audible, and on roentgen-ray the left auricle was prominent, the left ventricle was slightly enlarged, and the cardiac shadow was 12.5 per cent above the predictable size for his height and weight. A patient with a persistent hypertension showed slight enlargement of the left ventricle. The only case in which there was no evident cause for cardiac enlargement was the one described in detail above. The enlargement was 22 per cent above the predictable size.

A faint systolic murmur was audible over the precordium in 22 cases. It was usually loudest over the apex and of short duration. It varied in intensity with exercise and position and was heard best in the left lateral position.

Premature contractions were noted in five cases, in one of whom they were definitely known to have been present prior to the onset of the present illness.

A bradycardia and sinus arrhythmia were practically always present after the fever had subsided. They persisted as long as the abnormal electrocardiographic changes were demonstrable and occasionally for a longer period.

Laboratory Data: The blood counts, the percentage of "leukocytoid" lymphocytes and the heterophile antibody agglutination titer were not significantly different from those in the other cases in this series. Repeated erythrocyte sedimentation rates showed an increased rate at the onset in those with acute manifestations of the disease. The range was between 20 mm. and 66 mm. in one hour. After the temperature returned to normal and in the insidious cases the sedimentation rate was within normal limits and remained so in the great majority in spite of varying electrocardiographic findings. In a few of the cases who were observed for many months, there were occasional slight irregular rises in the sedimentation rate. The blood Kahn test was negative in all. Throat cultures were performed in 28 of the group and 13 were positive for *Streptococcus hemolyticus.* Through the courtesy of Dr. William S. Tillett, who furnished us with a strain of hemolytic streptococcus known to be highly active in the production of fibrinolytic substances, serial anti-fibrinolysin titers were performed in 23 cases according to his method.[54] Unfortunately, anti-streptolysin titers could not be done. In 16 of these there was unmistakable evidence of the presence of anti-fibrinolysins in the circulating blood. One plus reactions, present in six cases, were disregarded.

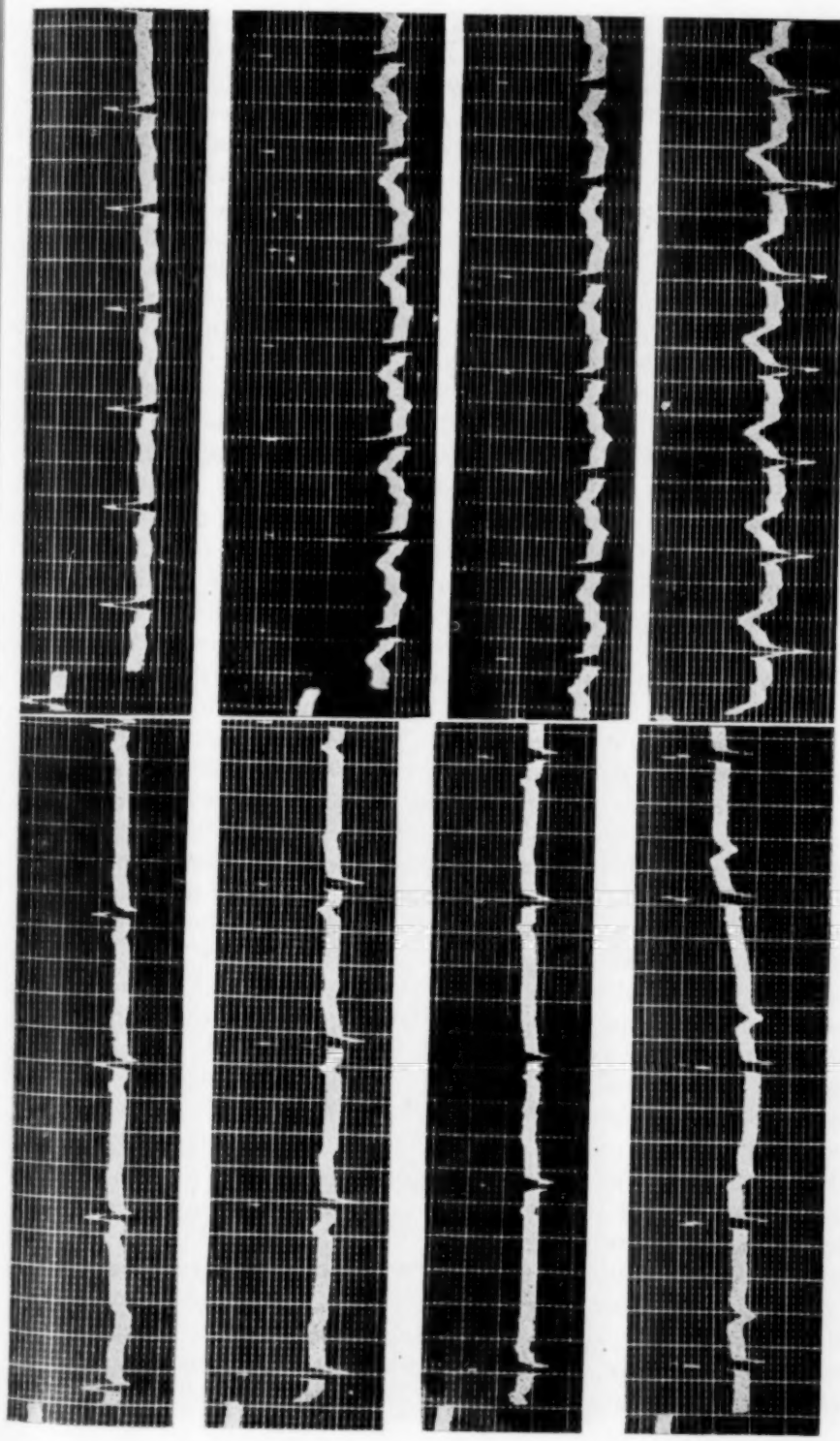


FIG. 8.

FIG. 9.

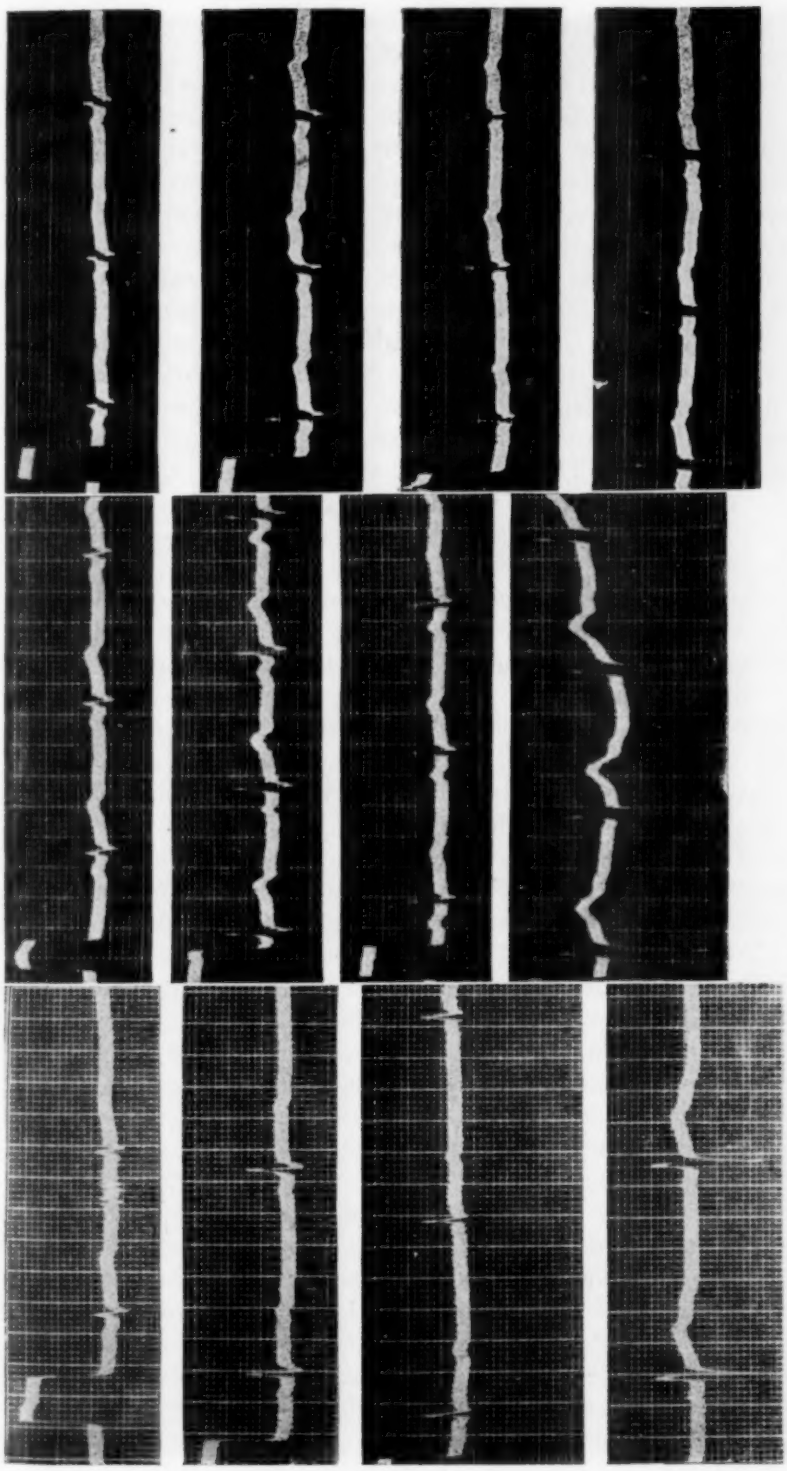
FIG. 8. Isoelectric T_1; low voltage T_2; T_3 upright; T_4 inverted.
FIG. 9. Low voltage T_1; T_2 and T_3 inverted.

Only one case was completely negative on repeated examinations. The anti-fibrinolysin titer usually reached its height in three to four weeks and then gradually decreased. The maximum titer was 4 plus in 11; 3 plus in 2; and 2 plus in 3. Positive throat cultures for *Streptococcus hemolyticus* were not always found in those cases with a rising anti-fibrinolysin titer.

Electrocardiograms: An electrocardiogram was taken within a few days after hospitalization. Routinely, the tracings consisted of the three standard limb leads and the apical chest lead, all taken in the recumbent position. Serial tracings, usually at five day intervals, were made in all who exhibited any deviation from the normal and in many whose initial electrocardiogram was normal. Abnormalities of the T-waves did not develop in any case subsequently, if they had not been present on the initial tracings. This was not true of the prolonged P–R intervals, although the majority followed this rule. There were records of electrocardiograms taken during a previous hospitalization in only two of the abnormal group and in both of these they were normal. The 53 patients with abnormal electrocardiograms could be conveniently divided into three groups: Abnormal T-waves, 39; prolonged P–R interval, 8; prolonged P–R interval and abnormal T-waves, 6. Changes in the voltage of the QRS complexes or in the S–T segments were not considered as of significance and were not listed as definitely abnormal.

The T-waves were either abnormally low, isoelectric or inverted (figures 8 and 9). When involved, the T-waves in all leads were affected but not to the same degree. T_1 showed the greatest change in all but three. In the latter, T_2 showed the greatest depression. In 13 cases with abnormality of T_1, the other T-waves were not abnormal but increased in amplitude as T_1 improved in voltage. Ten of the group were discharged from the hospital as soon as their tracings returned to normal. The remaining 29 were observed for longer periods and all exhibited a peculiar waxing and waning of the T-waves (figures 10 and 11). These repeatedly became taller or upright, and at times reached 1 mm. in amplitude but then reverted to their original appearance. Many of these cases were under observation for as long as six months without essential change in this cycle. It is possible that the 10 patients who were discharged soon after their tracings were found to be normal, might also have exhibited this phenomenon if further tracings had been taken. The abnormal T-waves were not appreciably affected by changes in position, respiration or large doses of belladonna.

The 14 exhibiting a prolongation of the P–R interval (figure 12), with or without associated T-wave changes, can be considered together as the behavior of the abnormal T-waves did not differ from that already described. Included in the group are two patients whose P–R interval increased from 0.16 sec. to 0.20 sec. without a change in the heart rate and which, a week later, returned to 0.16 sec. In the remaining 12 cases, the P–R interval ranged between 0.22 sec. and 0.40 sec. Second degree heart block occurred temporarily in two. The interval varied considerably during the period of observation and was unaffected by exercise or belladonna. Besides the two



a b c

FIG. 10. (a) Isoelectric T_1 and low amplitude of T_2.
(b) The same patient, five weeks later. Improvement in voltage of all T-waves. T_1 and T_2 are now within normal limits.
(c) The same patient, nine days later. T_1 is again markedly reduced in amplitude.

cases mentioned above, the P–R interval became normal in five additional patients in from 28 to 55 days, with an average of 40 days. In the remaining seven cases, a prolonged P–R interval was still present on discharge, four to nine months after the onset of their illness. The T-waves exhibited the same waxing and waning as previously described for the first group. They were within normal limits on discharge in four and persistent in two.

There were many other findings in the electrocardiograms which were considered to be either not definitely abnormal or preëxistent. There were many with low voltage of the QRS complexes. Five showed abnormal depressions of the S–T segments; one in all three leads and the others in $S–T_2$ and $S–T_3$. There were eight cases with premature contractions, five auricular in origin. Three of these were unassociated with other abnormalities and were not considered as significant. There were two cases of nodal rhythm which reverted to normal sinus rhythm during convalescence. One patient exhibited a short P–R interval and a prolonged QRS. He had a marked funnel breast, and there was no history of paroxysmal tachycardia. One patient, with the findings of an old mitral stenosis, showed a right ventricular preponderance.

The interpretation and the significance of the cardiac findings in this epidemic require critical evaluation. It does not seem likely that they were merely coincidental, in view of the large percentage of patients affected, the normal electrocardiograms in two of the patients prior to the onset of their illness and the appearance of prolonged P–R intervals during the course of the disease. These facts, however, do not eliminate the possibility of the coexistence of two independent diseases, especially the possibility that infectious mononucleosis was complicating rheumatic fever.

Although it is manifestly difficult to exclude a disease of unknown etiology without postmortem examination, the clinical picture had no resemblance to rheumatic fever as ordinarily encountered with the possible exception of the low-grade continuous type. There was no demonstrable latent period between the upper respiratory infection and the electrocardiographic findings and in spite of the persistence or increase in these findings, the patient never appeared ill. After the first few days there was a complete lack of concomitant evidence of rheumatic activity, such as fever, leukocytosis or increased sedimentation rate. They all manifested a persistent bradycardia after the acute phase of the illness had subsided. Polyarthritis or rheumatic nodules did not appear in a single individual. The systolic murmur, when audible, remained entirely unchanged throughout the period of observation. Moreover, the presence of hemolytic streptococci in the throats or cervical glands of patients with infectious mononucleosis was frequently described by the early investigators of this disease.[55, 56] Indeed, the German clinicians were quite uniformly of the opinion that a streptococcus was the important etiologic agent.[3] This view was based on the appearance of the throat, the predominance of streptococci in the flora of the upper respiratory tract and the occasional occurrence of a hemorrhagic nephritis or a scarlatiniform

a b

FIG. 11. (a) T_1 is normal and T_2 abnormally low.
(b) The same patient, three weeks later. T_2 is now inverted and T_1 abnormally low.

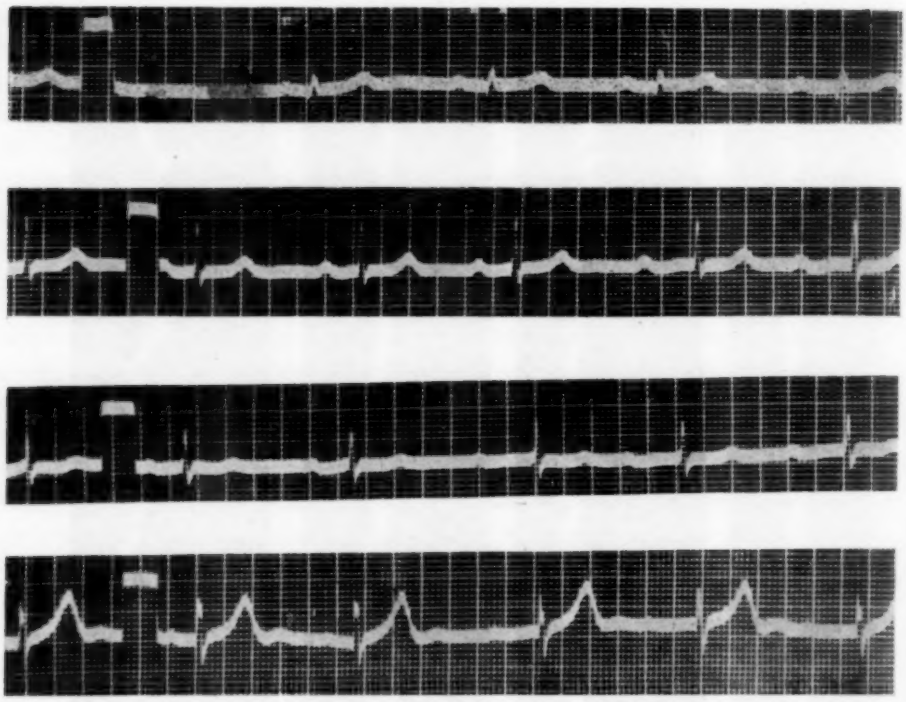


FIG. 12. The rate is 50. The P–R interval in Lead II increases progressively from 0.28 sec. to 0.40 sec.

eruption. In the more recent literature, cases have been reported that have been ushered in by a typical beta hemolytic streptococcus tonsillitis.[10, 87] A rising anti-fibrinolysin titer in the circulating blood of a significant number of the group does not necessarily indicate more than the frequency with which these organisms acted as secondary invaders in infectious mononucleosis. Besides, a rising anti-fibrinolysin titer can be present in streptococcus sore throat, scarlet fever or rheumatoid arthritis without evidence of cardiac involvement.

It is tempting to ascribe the condition to an overactivity of the vagus nerve. A varying degree of vagotonia could explain the bradycardia, the absence of fever, leukocytosis and increased sedimentation rate, the prolonged P–R interval and the waxing and waning of the T-waves. A soft, systolic murmur at the apex is not an infrequent finding in neurocirculatory asthenia and in psychoneurotics with similar symptoms. Symptoms of neurocirculatory asthenia are known to occur after acute infections and prolonged P–R intervals and abnormal T-waves have been described in this syndrome.[57] However, one would have expected belladonna to have caused these changes to revert to normal. Belladonna was exhibited in increasing doses until toxic manifestations appeared and in some cases for long periods. Atropine, hypodermically, was not used. Even if it were granted that atropine in large

doses, hypodermically, might have abolished the electrocardiographic abnormalities, this in itself would not eliminate the possibility of myocardial involvement as it can abolish the prolonged P–R interval in rheumatic fever, where myocardial involvement is the rule.[58] Atropine has also abolished a recurrent complete heart block, yet autopsy showed a badly diseased bundle.[59]

In conclusion, it can only be stated that although an autonomic imbalance is a strong possibility, actual involvement of the myocardium or its arteries cannot be excluded. Cases exhibiting the syndrome must be observed for many years and examined at post-mortem if possible, before the problem is finally elucidated.

12. Kidney. From the literature, the frequency with which the kidneys are involved in infectious mononucleosis varies greatly. Bernstein [10] in his 65 cases had none, whereas Tidy and Morley [55] reported an incidence of 6 per cent in the 270 cases which they collected.

In our series, there were 17 cases with abnormal urinary findings or an incidence of 3 per cent. The abnormal constituents were red and white blood cells, albumin, and hyaline and granular casts. They occurred either at the onset or within the first week of the illness. The course was uniformly benign with rapid return to normal, usually within seven to 10 days. None developed oliguria, edema, elevated blood pressure, cardiac dilatation, nitrogen retention or impairment of urinary function. In two cases of frank hematuria, the intravenous pyelograms performed during convalescence were normal.

In four cases there was macroscopic hematuria. It occurred at the onset of the illness in all, persisted for two or three days, and was then followed by microscopic hematuria for five to seven days. Microscopic hematuria alone was reported in seven cases. One patient with microscopic hematuria developed a morbilliform rash, while another later developed jaundice.

Increased numbers of white blood cells were found in all. In one case the urine was loaded with pus cells and suggested a pyelitis.

The albuminuria, which was present in all of the 17 patients, varied between 1 plus and 4 plus. It was not always proportionate to the hematuria, as in five cases there were no red blood cells found. In one of the latter, the albumin was 4 plus.

Casts were present in small numbers. They were usually of the hyaline variety. Granular casts were found in five cases.

Throat cultures were taken in five of the cases. Three were positive for *Streptococcus hemolyticus.* Anti-fibrinolysin titers were not performed.

13. Skin. An extraordinary variety of exanthemata have been observed in this disease. Although macular and maculopapular eruptions are the most common, erythematous, urticarial, petechial, purpuric and vesicular types have also been described.[10, 60] A case with lesions resembling erythema nodosum has been reported.[61] The frequency with which these eruptions have appeared has varied considerably. In the London epidemic of 1930 an eruption was present in practically every case,[62, 63, 64, 1 (f)] whereas in the re-

cent English epidemic [2] the incidence was only 4 per cent. In collections of sporadic cases, the incidence of eruptions has been as follows: Contratto,[33] 5.1 per cent; Sadusk,[60] 7 per cent; Bernstein,[10] 9 per cent; Lyght,[32] 17 per cent; Templeton and Sutherland,[65] 18.5 per cent.

Dermatologic manifestations occurred in 92 or 16 per cent of the patients in this epidemic. In an additional 16 patients a chronic dermatosis flared up or reappeared during the course of the illness. The eruptions were of many varieties and were often difficult to differentiate, especially when one variety blended into or followed another. We have classified the eruptions we have seen into the following types: (a) macular, (b) morbilliform and scarlatiniform, (c) maculopapular, (d) polymorphous, (e) nodular, (f) vesicular, (g) urticarial, (h) hemorrhagic, (i) alopecia.

a. Macular. This eruption appeared between the second and fourth day of the disease and was easily overlooked. There were two sub-types: a diffuse, red mottling, involving primarily the trunk and small faint-red macules scattered over the chest and abdomen and occasionally the extremities. The first type, of which there were four examples, faded very rapidly, usually within 24 hours. The second, of which there were five cases, closely resembled rose-spots, appeared in a single crop, blanched on pressure, were few in number and faded in a few days. There was no desquamation in either group.

b. Morbilliform and Scarlatiniform. This was the most frequent eruption and was also subdivided into two types. The first, consisting of 18 cases, was indistinguishable from the morbilliform rash of German measles. It appeared from the second to the fourteenth day of the disease. The lesions were numerous, diffuse, often confluent and involved both the trunk and extremities. As the clinical and hematological findings in German measles are so similar to those of infectious mononucleosis, the differentiation depended largely upon the Davidsohn absorption test. That it is impossible to distinguish between the two conditions in most instances without laboratory aid has been emphasized by other authors.[60, 65, 66] It is of interest in this connection that Glanzmann,[1 (d)] because of this similarity, postulated a close relationship between the viruses of the two diseases. It is in this group that the highest mononuclear counts were observed. In one case in which the disease occurred during convalescence from an acute cellulitis of the left foot, associated with lymphangitis and lymphadenitis of the femoral lymph nodes, the mononucleosis reached a peak of 95 per cent of a total white count of 19,300. In another, which occurred during convalescence from meningococcic meningitis in a patient who had the largest glands in this series, the mononucleosis was reported as 100 per cent of a total white count of 3,400. The second type, consisting of nine cases, was indistinguishable from that of classical scarlet fever, including a positive Schultz-Charlton test. As many of the clinical features of infectious mononucleosis, such as the sore throat, enlarged cervical lymph nodes, mild, generalized lymphadenopathy and a palpable spleen are, or can be, present in scarlet fever, the differentiation

depended upon the hematological and serological findings. The blood counts early in the disease were usually not conclusive, but serial blood counts revealed a progressive mononucleosis with large numbers of "leukocytoid" lymphocytes. This, in conjunction with a rising heterophile antibody agglutination titer and a positive Davidsohn absorption test, established the diagnosis. In eight of these nine cases, throat cultures were positive for *Streptococcus hemolyticus* and one wonders whether the scarlatiniform eruption was not due to secondary invasion by the streptococcus. *Streptococcus hemolyticus* was cultured from the throats of other patients with infectious mononucleosis during the period of this study, who did not develop this eruption, but it is well-known that streptococcus sore throat is accompanied by a rash in only a small percentage of cases. The positive Schultz-Charlton tests in every member of this group are difficult to explain on other grounds and militate against the possibility that an erythrotoxin is produced by the etiologic agent of infectious mononucleosis or by some other secondary invader. Unfortunately no anti-fibrinolysin or anti-streptolysin titers were performed in these cases. The eruption appeared with the onset of the disease in all but two cases, in whom it was delayed until the third and fourth day respectively. Typical desquamation occurred in all of the nine cases. Priest[67] described this phenomenon in one of his cases.

c. Maculopapular. There were 20 cases in this group. Although the lesions were discrete, they were not solitary and tended to have a patchy distribution on the upper and lower extremities as well as on the trunk. They were not so diffuse and symmetrically distributed as the morbilliform and scarlatiniform type, were more persistent and had an annular or circinate configuration. They closely resembled the eruptions of pityriasis rosea or secondary syphilis, but were considerably more pruritic than the usual examples of the former. The lesions usually appeared on the second or third day of the illness and in one of two forms. The first presented vari-sized, oval or rounded, scaling lesions with fine papular border and central clearing. They were quite profuse, especially on the extremities and were slightly more erythematous and had a heavier scale than the lesions of pityriasis rosea. The second variety exhibited vari-sized but larger, rounded, configurated lesions that had a tendency toward confluence with the formation of large patches. The centers were always macular and papular with a moderate or heavy scale and the borders at times showed signs of vesiculation. They were usually quite erythematous and were more pruritic than the first variety.

d. Polymorphous. There were 13 cases of this type. The lesions appeared from the first to the eighth day of the illness, and in a few were preceded by a morbilliform eruption. The lesions resembled those of erythema multiforme and were macular, papular, vesicular and occasionally bullous in character. They were profuse and involved the trunk, extremities, face and mucous membranes. The mucosal involvement, which was present at some time during the eruption in all, was occasionally severe, with extensive buccal

and gingival ulcerations. As a group, they represented the most serious skin manifestations and the patients were all very toxic.

e. Nodular. There were only two examples of this type. The lesions were typical of those seen in erythema nodosum and were confined to the anterior surfaces of the legs and knees. They appeared on the sixth and ninth day of the disease in these two cases and involuted with slight pigmentation and no scarring. In the case reported by Löhe and Rosenfeld,[61] the lesions appeared three and one-half weeks after the onset of the illness.

f. Vesicular. This group consisted of 11 cases, six of herpes labialis, four of herpes progenitalis and one of herpes zoster. In the case with herpes zoster, grouped vesicular and bullous lesions on an inflammatory base extended from the origin of the twelfth rib near the spine around the left flank to just below the umbilicus. The herpes progenitalis at times was difficult to differentiate from primary syphilis, especially when complicated by an erosive balanitis. The latter occurred in two of these cases, and in one a false-positive Wassermann reaction added further difficulties.

g. Urticarial. Pruritus was a common but evanescent symptom in all cases with skin manifestations and often preceded the eruption, serving at times as a help in the differential diagnosis. In five cases urticaria was the only eruption, while in several others it was present before the onset of the other types of lesions. The wheals were not of the giant variety, but of the small papular type. They appeared in crops, usually very early in the illness and disappeared in from five to 14 days. Dermographism was a frequent finding.

h. Hemorrhagic. Hemorrhagic skin manifestations were rare although carefully sought. A few petechiae were found in three cases, on the lower extremities, the chest and back, respectively. One was associated with epistaxis and petechiae on the soft palate. Purpura was not encountered.

i. Alopecia. In two cases small bald spots in the scalp occurred in association with the illness. No history of emotional shock or other predisposing factors was elicited. The lesions took several months to clear up completely. This small group may have been merely a coincidental alopecia areata. We have included them in the skin manifestations, because they may represent a neurotropic involvement akin to the herpetic lesions or a symptomatic alopecia as a part of a systemic infection.

As would be expected in so large a series, infectious mononucleosis occurred in soldiers suffering from a great variety of skin diseases, and the effect of this illness on the latter is interesting. The lesions of acute dermatitis, dermatophytosis, scabies, psoriasis and lichen planus remained unaffected while those of the seborrheic and eczema-dermatitis group showed marked exacerbations or recurrences.

A biologic false-positive serologic reaction for syphilis occurred in only one of the entire group, a patient with a polymorphous eruption and pneumonia. All four of the cases with eruptions in the series reported by Sadusk [60] had a transiently positive reaction for syphilis and the author

believes that it is more apt to occur in such cases. In his study, the tests were repeated at frequent intervals, in some cases as often as every other day, as compared to the single examination performed in the great majority of our cases. In spite of this, one would have expected a larger percentage of positive tests if such a marked relationship existed between the two phenomena.

In conclusion, it may be pointed out that the great majority of the skin manifestations were of the type usually classified as toxic eruptions of dermal origin, and represented varying degrees of reaction on the part of the skin to toxins or allergens. Medication could be excluded in their etiology. All were treated symptomatically with the exception of the severely ill ones, such as those with polymorphous or scarlatiniform eruptions. In all of these, the skin lesions were already present when sulfadiazine was exhibited.

14. Central Nervous System. Involvement of the central nervous system has been known since 1931 [68] and has been receiving increasing attention since that time. The situation, however, is confusing. The clinical picture is that of meningitis, encephalitis or both. It has been stated [69] that clinical signs of a serous meningitis may be present with normal spinal fluid findings and, conversely, that abnormal spinal fluids may be found in the absence of clinical signs of meningitis. It has also been reported [70] that the blood and spinal fluid findings may not occur until late in the course of the illness, so that early taps are not conclusive, and that clinical manifestations of infectious mononucleosis, such as lymphadenopathy and a palpable spleen, may not appear until the cerebral symptoms are almost gone.[71] In addition, owing to the enlargement of the cervical glands, pain in the back of the neck is not infrequent. When this is severe, it may be accompanied by voluntary rigidity and simulate a meningitis.

In nine of our cases because of severe headache, usually frontal, and mild to moderate nuchal rigidity, a spinal tap was performed. The spinal fluid was normal in six. Of the remaining three, the spinal fluid contained 12 lymphocytes but was otherwise entirely negative in one. In another patient, who was semi-stuporous on admission, it was under increased pressure, while in the third, it showed definite and striking abnormalities. The spinal taps were not repeated in eight patients as the presenting symptoms and signs disappeared rapidly. The last case is cited in brief.

An Italian prisoner of war, 24 years of age, was admitted with a history of severe frontal headache and vomiting of three days' duration. His temperature was 100.6° F., and a follicular tonsillitis was present. His temperature dropped to normal on the second day and although he remained afebrile for five days, the headache not only persisted but became violent. It was associated with hyperirritability, hypersensitivity of the extremities and mild nuchal rigidity. He developed a severe stomatitis and gingivitis, smears from which were positive for Vincent's organisms. The anterior and posterior cervical, the supraclavicular and axillary nodes were enlarged and tender. The liver and spleen were not palpable. Neurological examination was negative except for slight haziness of the optic disc borders. A spinal tap, performed on the ninth hospital day, showed 524 white blood cells, 517 of which were lymphocytes. The

globulin was 4 plus; sugar, 104 mg. per cent; chlorides, 540 mg. per cent; total protein, 284 mg. per cent; colloidal gold, negative; Wassermann reaction, negative.

His headache was greatly relieved by the puncture, but continued to recur in such severity that it had to be repeated at frequent intervals and always with marked relief. The pleocytosis and increased protein gradually decreased. The final tap, performed on the sixtieth hospital day, showed 64 cells, of which 63 were lymphocytes. The globulin was negative, sugar 67 mg. per cent; total protein 34.6 mg. per cent; colloidal gold, 1111000000.

The white blood cell count, shortly after admission, was 24,500 with a differential of neutrophiles 92 per cent, lymphocytes 7 per cent and monocytes 1 per cent. The white blood cells rapidly decreased to 9000, and the lymphocytes rose to 49 per cent, many of them "leukocytoid." The heterophile antibody agglutination titer rose to 1:224. There were no sequelae.

In summary, the clinical picture resembled that of lymphocytic choriomeningitis. The high total protein content of the spinal fluid would speak for cerebral involvement, although the neurological examination was negative for signs of localization. The initial spinal puncture, performed on the twelfth day of the disease, exhibited the most marked changes. The abnormalities of the spinal fluid then gradually diminished, the pleocytosis persisting for a longer time than the increased protein. A salient feature was the repeated relief of symptoms on withdrawal of spinal fluid and the relative well-being of the patient in spite of the severe headache.

The only other neurological manifestation was a severe, right brachial neuritis in a white officer, 29 years of age. He was admitted with a history of sore throat, chills, fever and dizziness of four days' duration. The pharynx was injected, the cervical glands markedly enlarged and the spleen palpable. His temperature on admission was 104° F. and then gradually subsided to normal on the fifth hospital day. The highest mononucleosis was 72 per cent and the maximum heterophile antibody agglutination titer was 1:1792. The brachial neuritis made its appearance on the seventh hospital day. He was treated with physiotherapy, large doses of vitamin B_1 and sedatives and the symptoms cleared completely in two weeks. A spinal tap was not done.

15. Other Organs. Although scleral injection was frequent, an actual conjunctivitis was recorded in only 12 instances. It occurred early in the course of the disease and was follicular in character. Rarely, the bulbar conjunctiva was fiery red and was accompanied by photophobia.

The salivary glands, testes and thyroid were not involved in any case.

16. Relapses. A relapse occurred in 50 patients or 9 per cent of the series. A second relapse took place in four. The duration of the afebrile period for the 54 relapses varied between one and 27 days. The interval between the attacks for all relapses is shown in table 6. Relapses were most frequent during the first week, when 65 per cent occurred. The relapses were usually milder than the original attack and followed the same pattern. Occasionally, however, they were more severe and new manifestations ap-

peared. In one case, a scarlatiniform eruption appeared with the relapse. The duration of fever in the relapse varied between one and 11 days.

17. Incubation Period. There is a wide divergence of opinion concerning the period of incubation.[10] The accumulation of reliable data relating to this period during the epidemic presented certain difficulties. In a disease as widespread as this and containing a great many insidious and mild cases, the possibilities for contact were obviously numerous. Acute attacks of infectious mononucleosis occurred in patients hospitalized for other conditions but here also, multiple exposures could not be excluded. It has already been stated that practically every patient in the hospital at the height of the epidemic showed some abnormal lymphocytes on blood smear. It was, therefore, decided to determine the interval between the arrival of the organization on the post and the earliest appearance of the disease among its members. There were many such organizations who arrived after the epidemic was in progress and in the great majority of these, this interval was

TABLE VI
Relapses

Days Afebrile	Number of Cases	Days Afebrile	Number of Cases	Days Afebrile	Number of Cases
1	6	10	1	19	2
2	8	11	2	20	2
3	5	12	0	21	1
4	6	13	1	22	0
5	4	14	1	23	0
6	2	15	2	24	2
7	2	16	1	25	1
8	2	17	2	26	0
9	2	18	0	27	1

nine days. In a few, cases occurred as early as seven or eight days. As the day of onset of the disease was usually not the day of admission to the hospital, the patient's history had to be utilized in most instances.

18. Laboratory Findings. A. Blood. Before discussing the hematological findings, it must be reiterated that the patients were admitted to the hospital in various stages of the illness, that a considerable number were asymptomatic and that many had but one or two blood counts. Our analysis, therefore, cannot be compared to the published collections of sporadic cases, which consisted almost entirely of those with such marked clinical manifestations that the disease was suspected or recognized and which were usually studied more completely.

The initial, total leukocyte count for the entire series was between 6,000 and 9,000 in 46 per cent, above this level in 34 per cent and below it in 20 per cent. A better conception of the behavior of the leukocyte count is gained by the exclusion of the insidious cases and the tabulation of the acute cases according to the day of the disease in which the primary blood count was performed. The typical sequence was an initial, transient leukocytosis,

varying between 10,000 and 20,000, or a normal count followed by a drop to either normal or leukopenic values. With these initial counts, the percentage of neutrophiles was usually normal or elevated. It rarely reached 90 per cent. A leukopenia and granulocytopenia at the very onset of the disease were unusual. This is at variance with the findings of Paul [72] in his sporadic cases. On the other hand, some sporadic cases have had a similar hemogram.[10, 33, 45] Blood counts in sporadic cases are usually not performed until four or five days after symptoms have appeared [10] and it is possible that a transient polymorphonuclear leukocytosis is missed. In the epidemics described by Glanzmann [1 (d)] and by Guthrie and Pessel,[1 (e)] an initial polymorphonuclear leukocytosis was the rule. Where leukopenia ensued, or was present on the initial count, the leukocytes gradually increased to normal and not infrequently to higher levels. The highest leukocyte count was 32,000 and occurred in two cases. The highest leukocyte counts attained in all

TABLE VII

Highest Leukocyte Count

Leukocyte Count	Percentage of Cases
Below 6,000	7.6
6–8,000	29.4
8–10,000	27.3
10–12,000	13.8
12–15,000	12.8
15–20,000	7.4
20–25,000	0.9
25–30,000	0.4
over 30,000	0.4

cases are shown in table 7. It will be observed that in spite of the factors already enumerated, the leukocyte count exceeded 10,000 in 35.5 per cent.

While the initial leukocytosis, when present, usually lasted for but a few days, the leukopenia tended to persist for a week or longer. The fall in the neutrophiles was more rapid than that of the total leukocyte count. There were 20 cases with counts of 4,000 or below. The lowest leukocyte count was 3,000. The leukopenia was due chiefly to a reduction in the absolute neutrophile count. Their number ranged from zero to 2900 cells, while their percentage varied between zero and 78 per cent. A concomitant reduction in the mononuclear elements was occasionally present. In four cases, the absolute mononuclear count was below 1,500. For the entire leukopenic group, the mononuclear cells varied between 777 and 3,485 and their percentages between 21 and 100 per cent. The average for these cells was 58 per cent.

The neutropenia was not confined to the leukopenic counts but was frequently present with normal and occasionally with markedly elevated leukocyte counts. There were 15 examples of leukocytosis with granulopenia. In one case, with a total leukocyte count of 19,300, the neutrophiles numbered

only 965 and in another, with 32,000 leukocytes, the neutrophiles were reduced to 3,840. In the entire series, there were four cases in which the total number of myeloid cells fell below 1,000. The actual figures for these cases were: 0; 60; 310; 965.

During the early stages of the disease, the eosinophiles were either absent or present in small numbers. During convalescence, they were frequently increased. There were 74 cases with an eosinophilia of 6 per cent or over. In 17 of these, however, other conditions were present that are frequently accompanied by an eosinophilia, viz. skin diseases, especially scabies and eczema, 12; asthma and hay fever, 3; uncinariasis, 2. The upper limit of the eosinophilia was 26 per cent in an asthmatic. Excluding this case, there were five with percentages of 15 or over for which no other cause could be demonstrated. The highest figure was 21 per cent.

The increase in mononuclear cells was usually evident after the third day of the disease but not infrequently this was delayed, so that the peak of the

TABLE VIII

Degree of Mononucleosis

Mononuclear Percentage	Percentage of Cases
Below 40	30
40–50	38
50–60	19
60–70	7
70–80	3
80–90	1.5
90–100	1.5

mononucleosis was not reached until the second or third week. The maximum degree of mononucleosis in our cases is shown in table 8. The reasons for the preponderance of low values have already been stated. If the insidious cases and those with but a single observation are excluded, the percentages more closely parallel those for sporadic cases.

The abnormal or "leukocytoid" lymphocytes need not be described as their distinctive features have already been discussed by many authors.[1 (d), 8, 28, 46, 73, 74] To have been included in this series, each case must have exhibited at least 10 per cent of the total leukocyte count in the form of these abnormal lymphocytes. In the great majority, the percentage of these cells was higher than 10 per cent and in many the percentage was 50 or more. In conjunction with the mononucleosis these cells usually diminished slowly over a period of weeks but were present in small numbers long after the mononucleosis had disappeared in those cases who were observed for long periods of time.

An anemia of any appreciable degree did not appear in any case in this series. The lowest recorded count was: red blood cells 4 million; hemoglobin 75 per cent (Sahli). Platelet counts and bleeding and clotting times were performed in only five cases and were normal in all.

B. Heterophile Antibody Agglutination. The highest titers in the 556 cases are shown in table 9. If an agglutination in a dilution of 1 : 112 or over is considered as significant, the test was positive in 62 per cent. The highest titer was 1 : 28,672. A rising titer was present in 236 cases. In judging these values, the fact that many had only a single determination and that no attempt was made to determine the maximum attainable titer, must be taken into consideration.

The time of appearance of a significant titer was erratic. Although it is true that a titer of 1 : 112 or higher was frequently observed during the first week of the disease, it, just as frequently, took two to four weeks for this to occur. A strongly positive reaction was invariably present early in the course of the disease in the group with maximum titers of 1 : 1,792 or higher. The rise in the titer was occasionally very abrupt and we have observed an increase from 1 : 56 to 1 : 448 or 1 : 896 within two days. In the cases that were under prolonged observation for either cardiac involvement or other conditions, there were several with titers of 1 :112 and 1 : 224 six months after the onset of the illness.

TABLE IX

Heterophile Antibody Agglutinin Titer

Titer	Percentage of Cases	Titer	Percentage of Cases
1 : 7	2	1 : 448	6
1 : 14	6	1 : 896	3
1 : 28	9	1 : 1,792	2
1 : 56	21	1 : 3,584	1
1 : 112	35	1 : 7,168	1
1 : 224	14	1 : 28,672	1

Davidsohn absorption tests,[30, 75] using both guinea-pig kidney and boiled beef red corpuscles, were performed at random, in doubtful cases with low titers and in patients with jaundice or with morbilliform eruptions. Although this test was strikingly confirmatory in many, it was not uniformly satisfactory. In a number of cases in which the guinea-pig kidney did not completely absorb the agglutinins, the beef red cells likewise failed to do so and in some of these, the latter absorbed a smaller percentage of the agglutinins than did the guinea-pig suspensions. In others, although there was no previous history of serum disease or recent injections of serum, both suspensions completely absorbed the sheep cell agglutinins. These cases were otherwise indistinguishable from the others in this series both clinically and hematologically and the titers before absorption were occasionally as high as 1 : 896. We have no explanation for these phenomena. One might infer that the heterophile agglutinins in this epidemic differed from that described for sporadic cases or that they varied in character with the stage of the disease. No experiments to clarify these suppositions were undertaken. Although Davidsohn absorption tests have been performed in a relatively small number of sporadic cases, similar irregularities have ap-

parently been encountered. Demanche [29] reported that in one of his cases of infectious mononucleosis there was no absorption by either antigen, while in another, an affinity for the beef red cells took place only after 24 hours. A study of the 78 absorption tests reported by Kaufman [13] reveals that 12 of the supposedly confirmatory tests were actually negative. In 10 of these, the sheep cell agglutinins were completely absorbed by both antigens. The test became positive later in the course of the disease in one of this group. Both of the other two showed complete absorption by the guinea-pig kidney suspension and incomplete absorption by the beef red cell suspension in one and no absorption in the other. There is some evidence [4, 76] that the titer of the normal Forsmann sheep cell agglutinins may increase before the development of the heterophile antibody typical of infectious mononucleosis.

C. Other Antibodies. The occurrence of a false-positive Widal test and increased agglutinins for various other bacteria have been reported.[25] In table 10 are shown the agglutinin titers for the bacteria tested and the number

TABLE X

Bacterial Agglutinin Titers

Titer	*E. typhosa*	*S. paratyphi A*	*S. paratyphi B*	*Br. melitensis*	Proteus OX19	*Past. tularensis*
0	54	67	59	19	11	3
1–20	3	2	1	—	1	—
1–40	6	1	1	—	—	—
1–80	2	1	3	1	—	—
1–160	4	—	2	—	—	—
1–320	1	1	3	—	—	—
1–640	4	—	3	1	1	—
1–1280	1	—	—	—	—	—
Total	75	72	72	21	13	3

of cases in which these tests were performed. The 75 cases were chosen at random. All had the Widal test but the other agglutinin titers were done in smaller and varying numbers. Significant agglutinins were found against all the bacteria tested, except for *Pasteurella tularensis.* However, only three sera were tested with this organism. Titers of 1 : 160 or higher were found in 13 per cent of the sera tested with *E. typhosa* and in 15 per cent of those with *S. paratyphi B.* In a number of cases, repeated titrations were done and it was noted that the titer rose abruptly and was transient. In one case, eight days after a negative test, the agglutinins were: *E. typhosa,* 1 : 1280; *S. paratyphi A,* 1 : 320; and *S. paratyphi B,* 1 : 160. In another case, a Widal of 1 : 640 decreased to 1 : 80 nine days later. All of the soldiers had received at least three injections of the Army's triple typhoid vaccine some time in the past. A so-called anamnestic reaction could explain the frequency with which high agglutinin titers for typhoid and paratyphoid were encountered in the group tested.

D. Kahn and Wassermann Reactions. Biologic false-positive reactions for syphilis in both the sporadic and epidemic forms of the disease are known

to occur. The first case was reported by Löhe and Rosenfeld [61] in 1928. Since that time, there have been numerous reports of such cases.[10, 36, 44 (b), 60, 63, 64, 66, 67, 77] Kolmer and his co-workers [77 (8)] compiled these publications and found transiently positive reactions in 20.9 per cent of 191 cases subjected to a Wassermann test and in 11.6 per cent of 146 cases subjected to a flocculation test. These figures, however, are misleading for several reasons. The two doubtful cases reported by Radford and Rolleston [78, 79] are included and the same three cases reported by Weber [63] and by Weber and Bode [77 (a)] are listed separately. Only two small collections with entirely negative findings [27, 80] are tabulated. Most vitiating is the inclusion of mere case reports for as Davis [79] points out, such cases enjoy a low threshold of publication.

The incidence in the small groups of sporadic cases reported has varied markedly as follows: Kaufman,[77 (f)] 3.6 per cent; Saphir,[77 (e)] 10 per cent; Sadusk,[60] 13 per cent; Bernstein,[10] 18 per cent. The epidemic cases have shown even more divergence. Tidy [62] stated that a transiently positive Wassermann reaction was present in about 50 per cent of the cases in the London epidemic of 1930 and Gooding [64] reported a positive reaction in 59 per cent of 27 cases from that epidemic. In the recent English epidemic the Wassermann and Kahn reactions were consistently negative in the many patients tested,[2] although the authors do not give the actual number of such tests.

These conflicting reports are probably due to variations in the sensitivity of the tests employed and the frequency and regularity with which they were performed. Many false-positives, according to Davis,[79] are technical and due to excessive sensitivity. Because adequate standardization had not yet become widespread, he considers as unreliable all papers on this subject written prior to 1930. Even with our improved methods, there is considerable fluctuation in sensitivity and a single positive report cannot be considered as valid evidence of a false-positive reaction. The diagnostic criterion he advocates is a repeatedly positive reaction to more than one kind of test or to the same test in two different laboratories that becomes negative after a few weeks or months without antisyphilitic treatment.

False-positive reactions ordinarily appear during the second week of the disease, although they can occur earlier.[60] The importance of frequent testing as against a single examination on admission was emphasized by Sadusk.[60] In his series, the incidence rose from 8 to 13 per cent when repeated tests at regular intervals were instituted. It is usually weak [79] and reverts to negative within two weeks, although occasionally it may persist as long as three months.[60] The Army recommends [81] that the patients be followed serologically and without treatment for a period of three months, serologic tests being performed every two to four weeks. At the end of this period, those that have reverted to negative are discharged from observation as non-syphilitic, those that are persistently positive are regarded as syphilitic, while those showing conflicting serologic reactions are subjected to further observation and study.

A blood Kahn test was performed in 263 patients. In the majority of cases, the blood was drawn at the end of the first week or during the second week of the disease. In the remainder, the duration of the illness was unknown owing to its insidious character or the test was done more than two weeks after its onset. The test was repeated in only 10 per cent of those with negative reports. A blood Wassermann test was performed in those with positive or doubtful Kahns and the tests were re-duplicated by our laboratory and by the Service Command Laboratory. Both tests were then repeated at frequent intervals.

The Kahn test was positive in eight and of these, the Wassermann test was positive in four and negative in four. The Kahn was doubtful in four and of these, the Wassermann was positive in two, doubtful in one and negative in one. None of the cases had been recently vaccinated. In four of the 12 cases, however, there was a history of a positive serologic reaction and antisyphilitic treatment in the past. Although these reactions were also transient, we feel that they should be excluded as they may represent the irregular behavior of weakly positive syphilitic sera. This reduces the incidence from 4.5 to 3 per cent. Because of the lack of repeated tests in those cases with initial negative reports, this cannot be regarded as the actual incidence of the phenomenon in this epidemic.

The reaction was transient in all. The shortest duration was nine days and the longest, 101 days. In those patients in whom the positive reaction persisted for longer than a few weeks, its intensity gradually diminished. The highest Wassermann titer was 12 units. Kahn verification tests revealed a biologic reaction in the three cases in which they were performed.

E. Bacteriological. Blood cultures were taken in 15 cases and were uniformly negative.

There were records of throat cultures in 104 patients. Of these, 61 were negative and 43 were positive for hemolytic streptococci, an incidence of 41 per cent. The anti-fibrinolysin titers in those cases with abnormal electrocardiograms have already been described.

Smears for Vincent's organisms were performed in 111 cases with positive findings in 74 or 67 per cent.

F. Miscellaneous. The laboratory studies carried out in the icteric group, the urinary findings and the changes in the cerebrospinal fluid have already been described in the appropriate sections.

Non-protein nitrogen, serum protein and serum calcium and phosphorus were determined in three cases and were all within normal limits.

The erythrocyte sedimentation rate was usually slightly or moderately elevated in the acute cases if tested during the febrile stage. The usual rate ranged between 12 and 35 mm. in one hour and fell rapidly to normal with convalescence. The highest rate was 79 mm.

19. Therapy. Sulfadiazine, in doses of 2 grams initially and 1 gram every four hours thereafter, was used in approximately half of the cases of the anginose type and in all with pulmonary symptoms, scarlatiniform

eruptions or positive hemolytic streptococcus throat cultures. It is difficult to analyze the results in a disease which is so variable in its severity, course and duration. It did not produce any spectacular response and there was no significant effect upon the duration of the disease in the treated group.

Penicillin was exhibited in one case not included in this series. He had a severe ulcerative tonsillitis, marked generalized lymphadenopathy, enlarged liver and spleen, mild jaundice and a morbilliform rash. Throat smears were positive for Vincent's organisms and cultures showed *Streptococcus hemolyticus*. He was given 2,340,000 units in a period of nine days with no appreciable effect on the clinical course or the hematological findings and only temporary disappearance of the positive throat cultures.

All acute cases were treated with bed rest, soft diet, forced fluids, sodium perborate mouth washes and small doses of aspirin. When jaundice was present, the patients were placed on low fat, high carbohydrate diets and multi-vitamin capsules.

Summary

A study of an epidemic of infectious mononucleosis in an army post is presented based on 556 cases observed during a period of 15 months. The diagnostic criteria and their limitations are discussed. An arbitrary standard, the presence of a least 10 per cent of the total white cell count in the form of abnormal lymphocytes, was used as the basis for the inclusion of the cases analyzed in this study.

The epidemic had many unusual features. Among these were the large number of asymptomatic cases, the incidence of the disease among the negro soldiers, the frequency and type of pulmonary involvement, the finding of electrocardiographic abnormalities in a large percentage, the number and variety of eruptions encountered and the irregularities in the results of the Davidsohn absorption test. In other respects, the disease closely resembled the sporadic form, the differences for the most part being due to the inclusion of insidious cases and the lack of serial blood studies in many of the patients.

The incubation period, as determined by the shortest interval between the appearance of symptoms and the arrival of the soldiers on the post, was seven to nine days. The disease attacked all ages of the select group involved. The percentage incidence at ages 18 to 20 inclusive was significantly greater and after age 38, significantly lower than the percentage strength of these ages in the army as whole, during the period of the epidemic. The divergence was most marked at age 18. Negroes were more susceptible to the disease.

The protean manifestations and the systemic nature of the disease are well illustrated, as are its contagiousness, its tendency to relapse and its generally benign course. The similarity between the pneumonitis complicating infectious mononucleosis and "virus" pneumonia was marked. The clinical picture and the liver function tests in the icteric group indicated that a dif-

fuse hepatitis was responsible for the jaundice. The impossibility of differentiating this group from infectious hepatitis without the aid of the heterophile antibody agglutination test was stressed. This was also true in excluding German measles and scarlet fever in those cases with eruptions characteristic of these diseases. Evidence is presented in support of the view that the scarlatiniform eruption was the result of secondary invasion by *Streptococcus hemolyticus*. Electrocardiographic abnormalities were frequent. The typical hemogram was an initial leukocytosis or normal count followed by a drop to normal or leukopenic values associated with a rising mononucleosis. Biologic false-positive serologic tests for syphilis were not of frequent occurrence. Sulfadiazine therapy had no appreciable effect upon the course of the disease.

No information was gleaned as to the etiology of the disease. Indeed, many other problems were raised by this study, especially the possible relationship between some of the clinical manifestations and secondary invasion with hemolytic streptococci, the nature of the pulmonary and cardiac lesions and the cause for the erratic behavior of the heterophile antibody agglutinins in the differential absorption tests. We hope that opportunity for future studies will clarify these problems.

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THE NUTRITIONAL STATUS OF JAPANESE PRISONERS OF WAR, BURMA 1945 *

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In May 1945, during environmental and nutritional investigations on Indian soldiers in South East Asia, an opportunity offered itself for the study of 29 Japanese prisoners of war captured near Pegu, Burma, and held in a forward divisional prisoner of war cage.

It was thought that such a study would be useful as it might indicate what types of nutritional disturbance one could expect to find in Allied soldiers held captive by the Japanese in South East Asia, and their rehabilitation could be planned accordingly.

Methods

Each Japanese prisoner of war was given a medical examination and stigmata of early nutritional failure, if present, were noted.

Blood and urine samples were collected from each prisoner of war and analyzed in a mobile biochemical laboratory. Blood hemoglobin, total protein and fasting serum vitamin C and serum chloride were measured, and urinary chloride, vitamin C, thiamine, riboflavin, and methylnicotinamide were estimated. The methods employed and the mobile equipment used in these studies have been described in detail by Johnson et al.[1] The criteria employed in diagnosing nutritional deficiency [2] differ but slightly from those of Johnson and his colleagues.[3]

Results

Medical Histories. When first seen the majority of the prisoners had been in the cage for three days and had eaten liberally of the food provided. They all consented to the examination and coöperated willingly. A Japanese interpreter was provided by Combined Services Detailed Interrogation Unit.

For three weeks previous to capture the majority of the prisoners had been living in the jungle on rice, rice and salt fish, or Burmese food. One had eaten nothing but mangoes during this time and another had been living on sugar cane. Both these men were very emaciated, and one had become pellagrous (see below).

Nine of the prisoners stated that during their service in Burma they had been treated in hospital for beriberi. One stated that, in August 1944, 80 per cent of his battalion who were north of Mandalay at the time, had come

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down with beriberi. It was also stated by another prisoner that because of the high rate of beriberi among the Japanese forces in Burma last year, all troops were ordered to take vitamin B_1 tablets every day.

However, of the 29 prisoners of war only five admitted that they had taken the tablets at all and only two had taken them regularly.

Physical Examination. Generally speaking there was little evidence of great weight loss. Three of the prisoners were emaciated, and about one quarter more had evidence of some recent weight loss. Many of them were covered with septic mosquito bites and thorn scratches. Fungus infections were negligible. A considerable number were obviously anemic. One had pellagra. He was emaciated, anemic, and had edema of his feet and ankles. His hemoglobin was 8.9 gm./100 ml. (40 per cent) and his serum protein, 4.4 gm./100 ml. He had had watery diarrhea for three weeks and presented atypical pellagrous skin lesions of the type described by Field.[4] Since he had been in the prisoner of war cage mild mental aberrations had developed.

TABLE I

The Biochemical Nutritional Status of Japanese Ps. O.W.

	Japanese Ps. O.W.	Indian Soldiers (2)	Canadian (6) and U. S. Army soldiers (1)
Hemoglobin Gm./100 ml.	12.0	14.4	16.8
Serum Protein Gm./100 ml.	5.6	5.7	6.4
Serum Chloride Meq/L	98.1	100	105
Urine Chloride Gm./hr. (fasting)	0.7	0.5	0.7
Serum Vitamin C Mg./100 ml.	0.1	0.13	0.8
Urine Vitamin C Mg./hr. (fasting)	0.6	0.4	0.8
Urine Thiamine Mcg/hr. (fasting)	9	13	13
Urine Riboflavin Mcg/hr. (fasting)	4	10	41
Urine M. Nicotinamide Mg./hr. (fasting)	0.6	0.5	0.5

Although none of the prisoners of war had skin lesions of vitamin A deficiency, six had chronic lesions of the eye with excess proliferative tissue and corneal scalloping or haziness, which probably dated from childhood. These lesions were much less marked than similar lesions which were very commonly seen among Indian soldiers, and which were considered to be signs of nutritional and environmental disturbances.[5] The commonest lesions seen were cheilosis, angular stomatitis and invasion of the cornea, which are associated with riboflavin deficiency. The cheilosis and angular stomatitis were marked and were present in 13 (38 per cent) of the prisoners of war. Other lesions seen were glossitis (four prisoners of war) and edema (two prisoners of war).

The ankle reflex could not be elicited in three of the prisoners who stated that they had had beriberi, but no other clinical signs were discovered.

Biochemical Findings. The biochemical nutritional status of the prisoners of war as compared with the Indian soldier and North American soldier is shown in table 1.

From these figures it can be seen that major deficiencies in blood hemoglobin levels and in riboflavin output existed. Serum protein and vitamin C levels and urinary vitamin C and thiamine excretions were below par.

Further analysis showed that only six prisoners had a hemoglobin level which fell within normal limits and 17 had anemia (Hb. less than 80 per cent). Seven of the 17 had hemoglobin levels below 70 per cent of normal. Five prisoners had normal protein levels, while six had levels below 80 per cent of normal. The serum proteins of three others were below the edema level (4.5 gm./100 ml.). The urinary excretion of riboflavin was extremely low and four prisoners (14 per cent) did not excrete any riboflavin whatsoever.

Comments

The low standard of nutrition found in the 29 Japanese prisoners of war is a reflection of the poor medical care given to the enemy in this theater of war. Although the number of men studied was not great, the results in part may be applicable to Japanese civilians and to Japanese forces in other theaters of operation.

The low hemoglobin and serum protein levels which were found are probably the result of malaria, poor dietary and hook-worm infestation. The thiamine levels were unexpectedly high especially when one considers that beriberi is not uncommonly seen in Japan and was certainly prevalent in Japanese soldiers fighting in the Burma theater of operations. Severe ariboflavinosis which was present, was probably the result of poor dietary intake. As yet we have not found any report in the literature of ariboflavinosis occurring in Japanese civilians or soldiers.

If the medical and nutritional care of the Japanese soldier has been as poor in other theaters of operation as it was in Burma, it is likely that considerable numbers of the enemy will require treatment for anemia, hypoproteinemia, and ariboflavinosis, as well as for other types of nutritional deficiency disease.

Summary

1. Japanese prisoners of war captured in Burma in May 1945, presented clinical evidence of anemia, hypoproteinemia and ariboflavinosis.

2. Biochemical studies showed low levels of hemoglobin, serum protein, serum vitamin C and urinary riboflavin.

3. Serum and urinary chloride, and urinary methyl-nicotinamide and thiamine excretions were within normal limits.

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BERIBERI IN JAPANESE PRISON CAMP*

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THESE observations on beriberi were made over a period of 34 months on approximately 8,000 Americans who had surrendered on Bataan and Corregidor. The 34-month period extended from April 9, 1942, with the surrender of Bataan, to January 30, 1945, with our release from captivity. We were handicapped by meager laboratory facilities, complete lack of cooperation of the Japanese officials, lack of supplies for records on these patients, inability to maintain follow-up records on the patients since they were moved in and out of the camp frequently, and also by the poor state of health of most of the medical officers. However, these obstructions to scientific study were over-compensated by abundance of clinical material. Hundreds of cases of any kind of vitamin deficiency disease were available for investigation at almost any time.

Beriberi was probably the most important vitamin deficiency disease encountered for several reasons. (1) Beriberi had the highest incidence, everyone in the camp having some form of beriberi at one time or another. (2) Beriberi had the highest morbidity. The disease was chronic in nature, incapacitating a soldier for months. (3) Beriberi had complications and sequelae, which were considered to be permanently disabling. (4) Beriberi was directly responsible for more deaths than any other vitamin deficiency disease.

The beriberi that was observed presented many novel features. It seemed far removed from the textbook picture.

APPEARANCE

Thiamine chloride deficiencies did not appear until late in the chronologic order of avitaminosis. A few cases of peroneal paresis and paralysis were seen in the first few months after capitulation. A maximum number of cases of peripheral neuritis appeared in January, 1943, after nine months of prison life. This was three to four months later than the appearance of manifestations of deficiency of the other vitamins in the B complex and about the same time as the onset of xerophthalmia, keratomalacia, and corneal ulcers from vitamin A deficiency. Scurvy was seen from time to time, but there were no large outbreaks. The chronologic order of appearance of all the vitamin deficiency diseases was carefully noted in hope of determining the storage capacities and the depletion periods of the body for the various vitamins. Of course, the appearance is also dependent upon the quantitative deficiency of each specific vitamin in the diet. Generally speaking, the diet was deficient in all vitamins. Also, the appearance depended upon the spe-

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cific pathogenesis. For example, in pellagra the mucous membranes and skin showed evidence of the disease almost as soon as deficiency occurred, but in beriberi degeneration of the nerves was slow and had progressed for several months before it became apparent. Therefore, we concluded that the late appearance of beriberi was not because of a large store of thiamine in the body, or because the diet was less deficient in thiamine chloride than in other vitamins, but rather because beriberi neuritis is a slowly progressive disease which appears several months after the provocative diet has been established. Actually, the store of vitamin B is less than that of other vitamins. The depletion period is usually stated to be from seven to 18 days on an entirely deficient diet.[1] The onset at times was hastened when the patient suffered from malaria or dysentery. Symptoms frequently were first noted after a malarial chill. This was not peculiar to beriberi. Pellagrous lesions were commonly seen in 24 to 48 hours after a malarial chill.

Diet

Beriberi was a natural consequence of our deficient diet. The diet varied from time to time but, roughly speaking, it was bad during 1942, improved during 1943, and was bad again in 1944. The diet issued by the Japanese was augmented occasionally by food purchased from the commissary, from the underground, from our own gardens, by what could be stolen from the farms, and by two shipments of Red Cross food. The total caloric value of the diet varied from about 900 to about 2,000 calories. The main staple was rice, but at times corn, camodies, casava and gabi were substituted for a portion of the rice. Vegetables, the leafy portions, fresh carabao meat, fish, oil, sugar and small amounts of fresh fruit were also issued. The diet was never considered adequate for vitamin B requirements. The rice that was issued was of medium mill. The pericarp which contains vitamin B was about half removed in the process. Adding the thiamine contained in this to the small amount in the leafy portion of the vegetables, and in an occasional dab of fresh meat, there was still a wide gap between this sum and the minimum physiologic requirements of 1.8 mg. per day.[2] Of course, this figure varies with caloric intake and the ratio of fat to carbohydrate in the diet. The thiamine chloride deficiency was exaggerated by the high carbohydrate and low fat content of the diet provided. It was the worst possible diet for one trying to sustain health on a low thiamine intake, since carbohydrates require more thiamine for their metabolism than either fat or protein, and also because fats have a thiamine-sparing action.[3] Attacks of diarrhea, vomiting, and malarial chills also increased the requirement. Consequently the incidence of beriberi was tremendous. Over 75 per cent, or 5,000 to 6,000 men at one time had painful neuritic feet.

Wet Beriberi

Two types of beriberi are considered, wet and dry. So-called acute beriberi is just one type of beriberi heart disease in which acute cardiac failure

is the salient feature. True wet beriberi is manifested by dependent edema due to deficiency of thiamine chloride. The exact mechanism involved in the formation of the edema is not known. Presumably it is not an edema of cardiac origin. The plasma proteins in these patients should be normal or at least above the critical edema level of 5.5 gm. per 100 c.c. of plasma.[4] Theoretically, thiamine chloride should precipitate a diuresis and cause the disappearance of the edema. This consideration is academic, since usually a diet that is sufficiently deficient to result in beriberi will also be low in protein. It is doubtful that we saw any true wet beriberi in our camp. The edema which appeared even in the days of fighting in Bataan, and through the entire prison life, was not dependent upon a thiamine chloride deficiency per se, for it appeared three to four months before the onset of polyneuritis. The diet had been low in protein content, and it is probable that the plasma proteins were below the critical edema level. Both hypoproteinemia and thiamine chloride deficiency were undoubtedly present in every edematous patient after a few months on the prison diet. Thiamine chloride alone, however, was unsatisfactory in treatment except in a few early cases, in which it seemed to precipitate a diuresis which may have been coincidental. It might be assumed that these patients probably had plasma proteins above the edema level and that thiamine chloride might have been necessary to establish a normal water metabolism. Later it had no effect on thousands of cases of edema. On the other hand, an increased protein intake for just a few days would improve the water balance. If a patient was developing edema during the day and having a nocturnal frequency of urination of 10 to 12 times a night, the ingestion of a small amount of protein would decrease the frequency by at least half Increased plasma protein and increased osmotic pressure of the blood plasma prevented escape of fluid into the tissues during the day, thereby decreasing nocturia. On the other hand, a patient with manifest and persistent edema would have a diuresis after ingestion of small amounts of protein. These changes in water balance were noted after eating only an 8 to 12 ounce can of fish (about 90 gm. of protein). We concluded that the edema was dependent upon a low protein intake and hypoproteinemia, not upon a wet beriberi. This does not preclude the existence of wet beriberi, but in these patients thiamine did not correct the water imbalance.

The edema was dependent in nature. The ankles were swollen at the end of the day and the face was swollen in the morning. Severity varied from subclinical or slight pitting to anasarca with fluid in all serous cavities. Everyone in the camp had some degree of edema at some time. The maximum number occurred in the first eight months, and particularly just after "the death march." The edema was worse at that time because of an orthostatic factor, since the men had been on their feet for days on a forced march. There was an improvement after arrival of the Red Cross packages in Christmas of 1942. There was then no change until late in 1943 when edema reappeared, but it improved with the second Red Cross shipment of

food in the Christmas of 1943. There was a steady increase in number of nutritional edema patients by 1944, until by January, 1945, about 40 per cent of those in the camp were so afflicted. The total protein content of the diet during the two bad years, 1942 and 1944, was calculated to be less than 30 gm. per man per day. Of this, 20 gm. were vegetable protein. We lived on 6 to 8 gm. of animal protein per man per day for over one year. This was once considered to be a physiologic impossibility. We admit our state of health was poor, but we managed to sustain life on this low protein diet. Beriberi heart disease, another etiologic basis for edema in a few patients, will be discussed later.

The course of the edema was entirely dependent upon protein intake. Usually edema did not inconvenience the patient, but a few required removal of fluid from the pleural cavities. Patients complained of heaviness of the feet and inability to get their feet into their shoes. There were no deaths from nutritional edema. The swelling did contribute to poor nutrition of the skin, which at times would macerate and weep, forming a large chronic ulcer.

The treatment consisted of extra protein feeding. The Japanese issued 10 cans of evaporated milk per day for the entire hospital, which at times had to be divided between 2,100 or 2,200 men. This futile gesture had no real effect. Mongo beans, peanuts, canned fish, and beef from the commissary and later Red Cross food were issued to the worst cases. Sometimes the results were dramatic, a patient losing from 50 to 75 pounds of edema in a few days. This was true also after intravenous administration of a few bottles of plasma. A salt-free diet was recommended but was difficult to enforce since it was extremely difficult to eat plain unseasoned rice and whistle-weed soup. At other times salty fish was the only source of protein, but the patient was encouraged to eat it regardless of the salt content. Fluids were curtailed because salt restriction could not be enforced. Diuretics, namely salyrgan and caffeine, were successful at times. Their effect was enhanced after intravenous use of plasma. Thiamine chloride had no effect on the water balance. Mechanical removal of the fluid was necessary at times. Occasionally the edematous fluid was evacuated via the bowel.

Dry Beriberi

Dry beriberi was almost always characterized by sensory symptoms of a symmetrical, ascending, peripheral neuritis. Motor disturbances were mild except in a few patients who developed foot or wrist drop. Painful feet or hands were predominant complaints. Motor and sensory symptoms did not usually exist in the same patient. Peroneal or radial nerve paresis or paralysis usually developed suddenly without going through the painful stage. Rarely did a patient progress from a painful state to motor paralysis, and when this occurred the pain would stop owing to development of a complete

anesthesia. Strangely enough, few men, less than 2 per cent in the entire camp's history, developed motor paralysis, whereas over 75 per cent had predominately sensory disturbances or painful feet. Other manifestations of dry beriberi were attributable to spinal cord lesions, apparently of the posterolateral tract; intra-ocular optic neuritis with gradual diminution of vision and optic atrophy; "beriberi spots," a skin lesion similar to erythema nodosum; and finally beriberi heart disease. Psychosis, breast tumors,* and transitory arterial hypertension were also seen, but a causal relationship was not established.

The first symptoms of a peripheral neuritis were stiffness, heaviness, or a tired feeling in the arches of the feet. At first we attributed this to going barefoot or wearing a homemade wooden clog. Soon there was aching in the arch and soles of the feet. This progressed to a dull, throbbing, deep bone ache in the whole foot. Soon sharp, shooting pain appeared, radiating from the arch to the tip of the toes. Burning pain, especially on the soles of the feet, paresthesia, and extreme tenderness next developed. These symptoms increased in severity until the patient was "half crazy." There was no relief. He would rub his feet or just look at them and cry. A common practice was for patients to sleep side by side, with heads in opposite directions, so that each could rub the other's feet. Soaking in water was a frequent, but not too successful remedy. Some unfortunate victims were unable to sleep, and their nights were spent in crying, moaning, and begging for relief. The pain soon spread up the legs to the knees, occasionally to the hips and a few even had pains and paresthesia across the abdomen, chest and scalp. After the feet were severely involved, pain developed in the fingers. Rarely did the symptoms advance above the elbows. In severe cases of long duration, the patient complained that the extremities were going to sleep or were dead. This anesthesia afforded some relief. The pain was worse during the daytime. It seemed to progress during the heat of the day and to improve with the coolness of the night or after a shower. The formation of edema in the legs eased the pain probably by a pressure anesthesia.

Complaints of a systemic character were insomnia, nervousness, anorexia, fatigability, palpitation, shortness of breath on exertion, and emotional instability, appearing simultaneously with the local symptoms. Gastrointestinal symptoms such as distention, excessive gas, foul breath and aerophagia were common complaints, but could not be evaluated because of the presence of many other possible causes such as dysentery, pellagra, worms and other intestinal infections.

Physical examination of such a patient revealed a thin, emaciated, malnourished male, weighing on an average 100 to 110 pounds. He was nervous, jumpy, and obviously suffering from acute pain. Examination of the affected parts revealed a mottled, erythematous skin. The soles of the feet and palms of the hands were often fiery red, an excellent picture of so-

* To be reported elsewhere.

called palmar erythema. Excessive sweating was noticed. Pronounced dermatographia was another sign of vasomotor disturbance. Occasionally the finger nails had disappeared or showed transverse grooves, usually two or three, while between them there was apparently normal nail. These grooves were the result of a period of small rations, and the normal nail of a period when the rations were better. We were reminded of the rings of a tree, corresponding to droughts and rainy seasons. There was a stocking and glove distribution of the sensory disturbance, usually to the level of mid-forearm and mid-thigh. Areas of paresthesia, hyperesthesia, pallanesthesia, hypesthesia, and anesthesia were found in the same extremities. Deep and superficial tenderness was severe. If we attempted to grab the patient's feet, he would jump and shriek as in mortal terror. Muscle tenderness was usually present but not severe. Muscle strength was very little changed. All patients were able to stand from a squatting position. At first the deep tendon reflexes were normal. At the height of the disease, about 40 per cent had 1 plus to 2 plus exaggeration of the deep tendon reflexes. No other abnormal reflexes were noted except in the groups which demonstrated spinal cord lesions or true paralysis. The gait was so unique, it was called the "Cabanatuan shuffle." It was protective because of the tenderness of the feet. The weight was placed on the outer side of the foot; each step was slow and deliberate; the patient looked carefully for a smooth place, then he gingerly placed his foot down, flinging his arms upward. Were it not for the suffering that it portrayed, it would have been a most amusing sight to see hundreds of men thus hopping across the compound.

Among this large group of patients with peripheral neuritis, about 50 per cent had visual complaints. Of this group, about 10 per cent had severe diminution of vision. These complaints appeared concomitantly with the development of severe neuritis and were distinct from the symptoms of xerophthalmia, keratomalacia, and corneal ulceration. It was simply a matter of inability to see with the usual clarity. Examination of the eyes demonstrated a gradually failing vision. Previously the visual acuity had been 20/20 or near normal. The loss was slow until 10 per cent, or about 500 men, had a vision of 20/200 or less. There was a narrowing of the visual fields and an enlarged blind spot. At first fundoscopic examination revealed a blurring of the disk margin. After two or three months there was more visual disability and a temporal pallor and macular degeneration. The height of the disability was reached after four to five months. The nerve head was white and a high grade optic atrophy had resulted. This process was considered to be an intraocular optic neuritis due to beriberi. There was no demonstrable loss of auditory acuity.

Another lesion, which was commonly seen in the patients with peripheral neuritis, was a skin lesion resembling erythema nodosum. This lesion was called "beriberi spots." We assumed that it was due to deficiency of thiamine chloride, but we were not at all certain of this. These spots were seen in hundreds of patients with peripheral neuritis. Their appearance co-

incided with the onset of the neuritic symptoms. The lesion was intracutaneous or subcutaneous. The site of predilection was the shin. It was symmetrical, slightly elevated, hot, tender and pink, extending over an area usually one inch to two inches in diameter. At times the lesions were fairly well circumscribed, appearing as an erythema nodosum. Again they were not circumscribed and appeared as a subcutaneous cellulitis. The lesions ran a rapid course, reaching their height in intensity in 24 hours. At times their appearance was preceded by a chill. Fever from 99° to 102 or 103° was usually present. The lesion was self-limited, resolving in 72 hours. Desquamation and brownish pigmentation of the skin followed resolution. There were no complications, except in a few cases where there was suppuration of the lesion. They were recurrent in nature; a man might have them every month to six weeks, almost in the same place, usually the shins. They disappeared as the peripheral neuritis improved. Although these patients certainly had a polyavitaminosis, the predominant nutritional disease at that time was beriberi. Therapeutic tests with ascorbic acid, niacin, and thiamine chloride were inconclusive. Even sulfanilamide was tried because of the inflammatory appearance. Most of us agreed that the "spots" disappeared as quickly with no treatment as with any of the drugs that were available. From our clinical observation, we concluded that "beriberi spots" were probably due to a thiamine deficiency even though therapeutic tests were not convincing.

A small number of patients, estimated to be 25, demonstrated involvement of the spinal cord. Here again, the etiology of the lesion was not clear. Although definite proof is lacking, clinically it was closely associated in appearance and course with beriberi. These patients usually showed a spastic paraplegia and more rarely a spastic quadriplegia. The onset was usually slow, taking a week or two, but at times was abrupt. These patients had a positive Romberg test, uncertain and ataxic gait, and positive Babinski reflexes. The sensory disturbances of peripheral neuritis were also present but were not necessarily maximum in degree. Attempts to discover some cause other than vitamin deficiency disease were unsuccessful. We concluded that the ataxia and lack of coördination were not dependent on the loss of sensory impulses but due to involvement of posterolateral columns of the spinal cord, probably resulting from beriberi.

Beriberi Heart Disease

Cardiovascular manifestations were encountered in the majority of patients with beriberi, but were extremely difficult to evaluate. The criteria for diagnosis of beriberi heart disease were (1) signs and symptoms of peripheral neuritis, and (2) symptoms referable to the heart without any other demonstrable cause. The criteria of dietary inadequacy are not listed because all men were suffering from malnutrition and were good candidates for any kind of vitamin deficiency disease. Also, a therapeutic test with

thiamine chloride would have been extremely valuable in establishing the diagnosis in these patients, but unfortunately our supply was so limited that this was denied to us. Consequently, the diagnosis was controversial at times. Undoubtedly it was diagnosed too frequently since there were meager laboratory facilities with which to discover other possible causes for the heart disease. These manifestations did not necessarily occur in the severest cases and usually no edema was present. All were of military age except for a few older civilians. Enlargement of the heart, either of the right side or left side, was not considered necessary for the diagnosis of beriberi heart disease. Extremely difficult was the differentiation of neurocirculatory asthenia and beriberi heart disease. Several well known neurotic patients developed beriberi and began to have cardiac complaints such as palpitation and dyspnea on exertion. The differentiation was almost impossible without an electrocardiogram and an adequate therapeutic test. We had nothing more than advice to offer these patients, but it was questionable whether to advise them to stay in or to get out of their beds.

The symptoms varied from dyspnea, palpitation, irregularities of the heart beat, and sudden attacks of pounding of the heart to the symptoms of congestive heart failure with orthopnea and prostration. Seldom was there complaint of precordial distress.

Examination of these patients revealed the heart to be usually of normal size. More than a hundred roentgenograms of the cardiac shadow failed to reveal any cardiac enlargement. The heart was usually hyperactive. A precordial pulsation was noted. The rate was from 130 to 140. Irregularities of the rhythm were frequently found, premature beats or extrasystoles, dropped beats, attacks of paroxysmal auricular tachycardia, and rarely a bradycardia of 30 to 40 per minute. In one group of 60 men that I observed, six had repeated attacks of paroxysmal auricular tachycardia. Almost every kind of arrhythmia was suspected, but without an electrocardiogram they could not be positively identified. Frequently a soft systolic murmur was heard over the precordium. At times a third heart sound was heard and a bifid apex impulse beat could be felt. Blood pressure was slightly lower than normal, ranging from 100 mm. Hg systolic and 60 mm. diastolic to 80 mm. Hg systolic and 40 mm. diastolic. Usually there was no evidence of decompensation. These were the findings in over 95 per cent of patients diagnosed as beriberi heart disease.

The second type of beriberi heart disease ran a chronic course, with enlargement of the cardiac shadow usually of the right side, and with cyanosis, hepatomegaly, râles in the bases of the lungs, dyspnea, dependent edema, and a fast, thready pulse. Only 20 to 25 patients were included in this group. The diagnosis was chronic beriberi heart disease with both left and right ventricular failure. Most of these patients died within a year without receiving adequate treatment. One patient who had been decompensated for about six months was finally given 10 mg. of thiamine chloride every day. Despite this the patient died. Autopsy revealed an enlarged

heart estimated to be about 500 grams. There was a dilatation and hypertrophy of both the left and right ventricle, but much more on the right. The auricles were slightly dilated. There was a large organized thrombus attached to the wall of the right ventricle, about 2 by 3 cm. This was the result of the long-standing decompensation, dilatation of the heart, and sluggish circulation. It was obvious why thiamine chloride did not help this patient. Digitalis was tried in most of these patients but, as expected, seemed to have no effect on the decompensation.

The third type of beriberi heart disease manifested itself in acute dilatation of the heart, pulmonary edema, and death within a few minutes to 24 to 48 hours. These patients had peripheral neuritis and usually no edema. They occasionally had symptoms referable to the heart, such as palpitation or poor exercise tolerance. One minute prior to the onset they were walking around and the next minute they collapsed. We felt that exercise was extremely dangerous to patients with peripheral neuritis since their hearts were already weakened. Acute cardiac death occurred in young as well as middle-aged men. The estimated number of these deaths was 50; undoubtedly, the figure would have been higher if painful feet had not prevented them from walking.

Beriberi heart disease was manifest in three ways: (1) Normal size heart with arrhythmias and decreased tolerance to exercise. (2) Enlarged heart with chronic left and right ventricular failure. (3) Acute cardiac dilatation, pulmonary edema and death.

Conclusions: (1) Enlargement of the heart is not to be expected in the majority of cases of beriberi heart disease. (2) Thiamine deficiency may be the cause of almost any type of cardiac arrhythmia. (3) Both left and right ventricles are involved in congestive heart failure in beriberi heart disease. (4) Digitalis is without benefit in the treatment of beriberi heart failure. (5) Beriberi heart disease is an acute medical emergency which must be treated energetically to prevent secondary irreversible damage or death.

Course

The course of beriberi patients depended upon the severity of the lesions and complications. Except for the deaths of the patients with cardiac manifestations they continued to live although severely incapacitated at times. There were exacerbations of the symptoms during the low ration period and improvement with a better diet. It was as long as four to six weeks between the increase in ration and improvement in symptoms. After several years the patient seemed to have accustomed himself to a lower vitamin B_1 intake.[5] Another explanation was that thiamine chloride was synthesized in the gastrointestinal tract after a period of time. Despite this, about 15 per cent of the men complained of hyperesthesia, aching of the feet, deep and superficial tenderness even at the time of release in January, 1945. The common sequelae were optic atrophy, a few cases of spinal cord lesions, muscular atrophy, paralysis of leg muscles, and sensitivity of the feet.

Diagnosis

The diagnosis of beriberi was obvious after the first symptoms had been evaluated. A typical peripheral neuritis was present, i.e., ascending and symmetrical. Almost all the complaints were of a sensory nature. We could not explain why these patients did not show more signs of motor involvement. Orthopedic causes, metabolic neuritides, and vascular disease were ruled out. The etiology was based on one common denominator, vitamin deficiency disease. Thiamine chloride deficiency was probably the cause for the manifestations that have been discussed, although there is a good deal of question about the beriberi spots and the spinal cord lesions.

Treatment

Little can be said of the treatment of these patients in our camp. The minimum therapeutic dose of 20 mg. of thiamine chloride per day was rarely available for the patients. For over a year 1 to 2 mg. per day was the standard dose. Many times there was no synthetic thiamine available. After the Red Cross supply of 1943 arrived, there was a sufficient amount to give 10 to 20 mg. and occasionally over 20 mg. per patient per day for a 10-day course. By that time most of the men were cured or markedly improved by the increased diet. Exceptions to this were the patients with foot drop who showed almost no improvement despite the administration of 20 mg. of thiamine per day for six months or longer. In the early days we used a yeast culture made from rice, sugar, and brewer's yeast. Each man received from 6 to 8 ounces a day of this preparation. Calculating from the yeast cell count each patient received about 3 mg. of thiamine chloride per day from this source. Small amounts of rice polishing, tiki-tiki, and brewer's yeast were available. Extra foods were shunted to these men. Actually, Red Cross foods and the special meat issue were paramount in the improvement and cure of these patients. Quinine had a deadening effect on the pain in the extremities. That drug also was so scarce it had to be given only for malarial chills and fever. Narcotics were conscientiously withheld but it was difficult to keep from giving morphine to a friend who was crying from acute agony.

Special Study

There was only one small group of Americans who were adequately treated during the acute illness. This was a group selected for study by a Japanese doctor. A board of seven American doctors conducted the study under the serveillance of the Japs. It was a therapeutic response experiment. It was far removed from a scientific study; however, the patients benefited from the extra vitamins that were made available. Ninety-six of the severest cases of painful feet were selected for this study. They all demonstrated the typical "Cabanatuan shuffle" and sensory manifestations of symmetrical ascending peripheral neuritis of beriberi. It has been stated previ-

ously the typical lesion was a sensory disturbance with usually little to no involvement of the muscular strength. No patients with cord degenerative lesions, muscular paralysis, active malaria, or dysentery were included. Complete physical and neurologic examinations were made on all patients and recorded. Blood count showed routinely a secondary hypochromic anemia and leukopenia of from 3,000 to 5,000. The urine was normal. Roentgenograms of the long bones showed 1 plus to 3 plus osteoporosis. This was still present three to four months after our liberation. This raised the question whether vitamin deficiency disease plays a rôle in the process of osteoporosis. It may tend to exaggerate the imbalance of calcium-phosphorus in a deficient diet. Six foot roentgenograms of the chest revealed a heart shadow of normal size. Despite this finding almost every man complained of dyspnea and palpitation and occasional attacks of paroxysmal auricular tachycardia. Fractional gastric analyses showed usually no free hydrochloric acid in the fasting specimen and low hydrochloric acid in the others. Spinal fluid on these patients was normal as to dynamics and cytology. Increased spinal fluid pressure is sometimes given as a diagnostic aid in beriberi but was not a finding in our patients. Ophthalmoscopic examination revealed an optic atrophy in a majority of the patients. Visual acuity was usually less than 20/200. In a few patients blood chemical tests were made by Japanese technicians but were never reported to our board.

There were eight groups of 12 men each. Each group was treated differently as listed below. The medication was given for a three-week period. The dosage shown is the daily dose per man.

Group I (a) 6 men	10 mg. thiamine chloride intrathecally 10 mg. thiamine chloride subcutaneously
(b) 6 men	20 mg. thiamine chloride subcutaneously
Group II	60 gm. powdered brewer's yeast 10 mg. thiamine chloride subcutaneously 1 c.c. liver extract intramuscularly
Group III (completely treated)	20 mg. thiamine chloride subcutaneously 60 gm. brewer's yeast 1 c.c. liver extract intramuscularly 250 mg. niacin 200 mg. ascorbic acid subcutaneously 1 c.c. B complex preparation subcutaneously 60 c.c. cod liver oil orally 4.5 mg. riboflavin orally 1 gm. calcium phosphate orally
Group IV	60 c.c. cod liver oil orally 1 gm. calcium phosphate orally
Group V	200 mg. ascorbic acid subcutaneously
Group VI	250 mg. niacin subcutaneously
Group VII	4.5 mg. riboflavin orally
Group VIII	Control. This group received placebos.

All of these patients were issued the same diet. The diet at that time consisted approximately of 20 gm. of animal protein, 350 gm. of rice, a 3 ounce serving of cooked mongo beans and varying amounts of vegetables, 10 gm. of sugar, some oil and occasionally bananas and limes. The caloric value was approximately 1600. The patients were needlessly advised to eat all the ration and nothing else.

The patients were examined and questioned every day for the first month. The results were recorded as to severity from zero to 4 plus. A schematic drawing was kept on each patient indicating the areas of anesthesia, hyperesthesia, paresthesia, and degree of tenderness, reflexes, strength, and appetite. After the first two months, examinations were made every week; the observation period lasted for a total of five months.

Despite our high hopes and enthusiasm we were unable to find any startling results. There were no clear-cut differences in the amount of improvement in the first two months. All the groups, and even those not included in our study, showed the same amount of improvement during this period. Soon afterward, however, the patients in groups I, II, III, or those receiving thiamine chloride or B complex, showed an improvement of the appetite, less insomnia, less irritability, and more emotional stability. The pulse rate dropped from around 130 to 140 down to 90 to 100. Exercise tolerance improved. Less tremor of the hands and feet was noted. There was no perceptible change in the pain in the hands and feet at this time. However, some men who had progressed to the stage of anesthesia of the extremities complained that they were "waking up." This proved to be a common finding. Thiamine chloride seemed to cause an increase in the pain before improvement set in. Dyspnea, palpitation and arrhythmias of the heart were other findings which showed an early improvement. It was not until four months that group III, or the completely treated group, evidenced slightly more improvement in the sensory manifestations; this consisted of less pain and tenderness in the extremities. The sweating, dermatographia, plantar and palmar erythema were lessened. The optic nerve lesions and visual acuity were not changed by the treatment. Group II, B complex, was next in the amount of improvement. Group I patients received thiamine chloride alone and showed no more improvement of the pain in the extremities than the control group. There was no choice to be had in the remaining groups. All showed a gradual improvement similar to that shown in the entire camp.

Conclusive results were not obtained because the patients were still issued a border-line starvation diet. The dosages and length of treatment were inadequate. The neuritis had persisted for about six months prior to the time of treatment. Extensive nerve damage had been done; consequently the repair was slow. However, we hoped that a temporary saturation of the patient with thiamine chloride had been reached in the treatment of the first three groups. One man from group III, the completely treated group, clarified this point for us. On the day following the end of three weeks' treatment, he had a malarial chill and fever; the next day pellagrous lesions, hemorrhagic blebs, appeared on both legs. Within two days he had a complete bilateral peroneal paralysis. With the appearance of the motor disturbance, his sensory complaints quickly disappeared. The pellagrous lesions soon responded, but the foot drop persisted for over a year and a half despite specific therapy.

Conclusions

1. Thiamine chloride first corrected the anorexia, nervous manifestations, tachycardia, arrhythmia, and improved the exercise tolerance of the heart in patients with beriberi.

2. Beriberi peripheral neuritis responded sooner to the entire B complex than to thiamine chloride alone.

3. Intrathecal route of administration was no more efficacious than subcutaneous injection.

4. Complete saturation of the body with thiamine chloride was not attained by a short course of large doses.

5. More vitamins can still be bought in a grocery store than in a drug store.

6. There may be nutritional causes of polyneuritis other than lack of thiamine.

7. Palmar and plantar erythema are consistently seen in dry beriberi.

8. "Beriberi spots" is a newly described skin lesion probably due to thiamine deficiency.

9. Motor manifestations are often minimal or lacking in beriberi peripheral neuritis.

10. Posterolateral column degeneration of spinal cord in malnutrition is probably due to lack of vitamin B_1.

11. An irreversible optic atrophy may result in severe beriberi.

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SUDDEN DEATH IN RHEUMATIC FEVER *

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Introduction

Abrupt cessation of heart beat, as distinguished from gradual failure, involves mechanisms of which we know little.[1, 2] Sudden death occurring in this manner often finds no adequate pathologic explanation, although there is usually evidence of cardiac and aortic disease. In searching for a plausible general hypothesis, that of acute circulatory impairment in the heart, lungs, or brain-stem appears not unattractive. Although vascular occlusion by emboli, by thrombi forming in damaged areas, or by gradually progressing sclerosis has long engaged the attention of pathologists, awareness of functional vascular changes, in part, perhaps, referable to the autonomic nervous system [3] of acute "hyaline" thrombosis, and of acute lesions in arterial walls is more recent. Such changes have been studied experimentally in anaphylaxis and related phenomena, and it is noteworthy that acute arterial lesions may be difficult to distinguish from those designated as arteriosclerosis. Rich and Gregory have presented evidence suggestive of a close parallelism between the pattern of "rheumatic fever" and that of anaphylactic hypersensitivity. We have recently reported pathologic findings which accord well with that hypothesis. One might, therefore, expect to find instances of sudden death in rheumatic fever. Although the literature contains little on this topic, it is the considered clinical opinion of one of us that such occurrences are more frequent than is generally realized. It seemed desirable, therefore, to report three cases of sudden death in patients at the rheumatic fever unit of this hospital.

Source of the Material

The Rheumatic Fever Unit of the U. S. Naval Hospital, Corona, California, is the source of the material contained in this report. From a caseload of 7165 rheumatic fever patients observed over a period of 18 months, 13 deaths occurred. Three of the 13 deaths occurred suddenly and dramatically. The three cases of sudden death occurring in the course of very mild rheumatic fever are the basis of this presentation.

Case Reports and Pathological Findings

Case 1. J. C., a 28 year old male of medium height and sthenic build, was admitted to the sick list November 10, 1943, complaining of painful and swollen knee joints. There was no history of a previous attack of rheumatic fever. He had an

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attack of tonsillitis three weeks previous to the onset of the painful joints. Examination revealed very slight fever, migrating joint involvement and an elevated blood sedimentation rate. With bed rest and salicylate therapy he improved. He continued upon treatment with rest and mild bed exercises. On January 20, 1944, physical examination was essentially negative. He complained of mild joint pain unaccompanied by swelling or tenderness. At that time the blood sedimentation rate was 45 mm. per hr. (Westergren). The electrocardiograms were normal, except for an inverted T_3 wave. There was no Q_3 wave present (figure 1). He was treated with

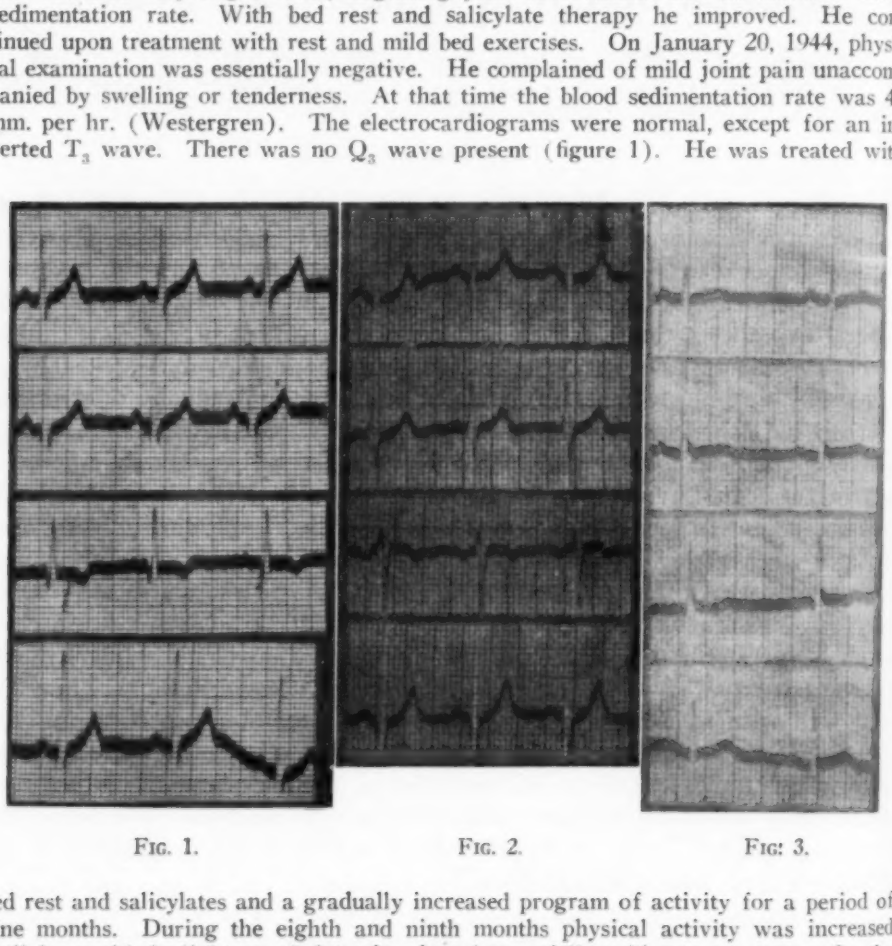

FIG. 1. FIG. 2. FIG: 3.

bed rest and salicylates and a gradually increased program of activity for a period of nine months. During the eighth and ninth months physical activity was increased until he could do light ward duty for four hours daily without symptoms. In the seventh month of illness a faint apical systolic murmur was heard in the recumbent position only. In the ninth month when no signs of rheumatic activity persisted, except a blood sedimentation level of 15 to 20 mm. per hour (Cutler), it was felt wise to remove badly diseased tonsils. The patient was prepared for tonsillectomy by giving 25 grains of sodium salicylate combined with 10 grains of sodium bicarbonate every four hours for one week, and 15 grains of sulfathiazole t.i.d. for two days prior to operation. Preoperative medication consisted of nembutal, gr. 1½ and atropine sulfate, gr. 1/150. Under novocaine local anesthesia tonsillectomy was performed without difficulty and without any change in the patient's circulatory state. The patient walked from the operating chair to a wheel-chair, and was put to bed upon the ward. Patient looked well and felt well. Suddenly, one hour later, the patient became pale, then cyanotic and was found to be pulseless. No heart beat was audible. Respirations continued for several minutes longer. Efforts at resuscitation were futile.

Gross pathologic examination showed the following noteworthy findings: There was marked cyanosis of lips and nail-beds. Upon examination of the thoracic contents, the heart was found to measure transversely 17.0 cm., and the internal diameter

of the chest 30.0 cm. The pericardium was moderately thickened and contained a few c.c. of blood-stained fluid. The heart weighed 540 gm. There were numerous small subepicardial hemorrhages. The circumference of the tricuspid orifice was 11.0 cm., of the mitral orifice 11.0 cm. The tricuspid and mitral leaflets showed streaky thickening. One mitral cusp was markedly retracted. There were what appeared to be calcified plaques on the aortic cusps. The base of the aorta was greatly thickened. There was gross distortion and narrowing of the right coronary ostium. Both coronary arteries and the main branches were grossly thickened and the lumen appeared almost entirely occluded. The lungs showed marked congestion in some areas, while other areas appeared relatively bloodless. There was no obstruction in the bronchial tree or in the main pulmonary arteries.

The microscopic findings of interest were, first, accumulation of relatively homogeneous extracellular material in the coronary arteries and at the base of the aorta. Masson stains showed this material to be largely neutrophilic, though intensely acidophilic (fibrinoid?) areas were present. Elastic tissue stain of a coronary artery showed that this material was largely intramural. Aggregates of large Aschoff-like cells were noted in some areas, and there was endothelial proliferation in others. Endothelium-lined spaces were present, and were probably new vascular channels. Small coronary branches showed marked cellular proliferation. The valvular and mural endocardium showed accumulation of hyaline material similar to that in the arteries. Collections of "Anitschow myocytes" were scattered throughout the myocardium. Similar cells were conspicuous at the base of the aortic cusps. A lung section showed an artery occluded by material similar to that seen in the coronary arteries, but containing more cells and evidence of organization, and the appearance of the surrounding lung was that of organizing infarct.

Anatomical Diagnosis: Rheumatic arteritis, coronary artery insufficiency, extreme; rheumatic myocarditis, endocarditis, and pericarditis; pulmonary infarcts, small, multiple, due to pulmonary arteritis.

Case 2. F. C., aged 22 years, of medium height and weight, was examined numerous times in the Navy, including a very carefully recorded examination prior to a herniorrhaphy in 1940. No evidence of heart disease was found. He went through a strenuous tour of duty in the South Pacific during 1943 and early part of 1944. Upon application for an increase in insurance, the consultant at a U. S. Naval Base Hospital reported: "there is a history of rheumatism with swelling of the knees at the age of 14; examination shows a loud systolic and a slight aortic diastolic murmur, heard best at the second right interspace; the blood pressure is 160 mm. Hg systolic and 60 mm. diastolic; patient has an old rheumatic aortic lesion well compensated." "Recommend restriction of extreme strain and over-exertion." He was returned to the continental United States on October 18, 1944, as he complained of shortness of breath while engaged in amphibious training. He was admitted to the sick list on that date. On November 3, 1944, careful physical examination showed slight cardiac enlargement, a systolic murmur at the base of the heart transmitted into the neck vessels but unaccompanied by a systolic thrill, an aortic diastolic murmur heard best in the third left interspace, and a systolic murmur heard best at the apex of the heart and transmitted well into the axilla. The exercise tolerance test showed a resting pulse of 72, after exercise 116 and after one minute rest the pulse was 78. There was no cyanosis and no dyspnea. The temperature and pulse remained normal during 18 days' observation. The electrocardiograms were within normal limits (figure 2). The teleroentgenogram showed 25 per cent enlargement according to the Ungeleider table. The blood count, urinalysis and sedimentation rates were within normal limits. The Kahn test was negative and there were no stigmata of syphilis. He was active on the ward following a program of gradually increased activity. On November 20, at 10:30, he was assigned outside duty, as there were no signs of rheumatic activity

and no signs of limited cardiac or pulmonary reserve. A review of his health record showed no evidence of an active rheumatic process since enlistment within the Navy. It was assumed the heart disease was a well compensated residuum of the rheumatic activity which occurred at the age of 14. The patient went canoeing at noon on November 20, 1944, in company with a qualified life-saver. The patient, who was paddling stern, without any outcry suddenly fell overboard. The patient did not rise to the surface, although he was known to be a strong swimmer and experienced boatman. The body was recovered six hours later.

The *gross pathologic examination* was essentially negative except for the heart and lungs. The lungs floated, and there was crepitation throughout. There was a large amount of fluid in the trachea and bronchi. There was vegetation material in the nares and in the trachea. The pericardium was not thickened and contained 30 c.c. of straw-colored fluid. The heart weighed 500 gm. The right ventricle was dilated; the left ventricle was contracted. The right ventricular wall measured 6 mm., the left 16 mm. The tricuspid orifice measured 10 cm. in circumference; the mitral orifice 8 cm. The tricuspid leaflets were fused and retracted. The mitral leaflets were greatly thickened, fused and the free edge was extremely hard. The aortic valve cusps were thickened and curled. The circumference of the aortic orifice was 7.0 cm. The left coronary artery showed a sclerotic patch near its origin and at 5 cm. from its ostium was greatly narrowed. There was a discolored softened area measuring 30 by 20 mm. in the anterior wall of the heart. The anterior descending branch of the left coronary, leading into this area, appeared occluded by edema of the arterial wall. There were a number of sclerotic patches in the aorta at its origin and elsewhere.

Microscopic pathology: The softened area just described contained an excessive amount of blood, apparently largely intravascular, and a rather curious scattering of eosinophiles. Elsewhere in the myocardium were occasional collections of fibrocytic cells and Anitschow myocytes. The valves showed a remarkable chronic active process, characterized by calcification in some areas, and by vascularization and infiltration by round and large mononuclear cells in others. The aorta showed striking cellular accumulation. There was considerable focal edema in the coronary arteries and endocardium, with fibrosis around coronary arteries. How far the acute edema in these arteries was attributable to submersion could not be determined.

Anatomical diagnosis: Chronic rheumatic endocarditis involving the aortic, mitral and tricuspid leaflets; acute rheumatic arteritis with occlusion of the anterior descending branch of the left coronary artery, and submersion.

Case 3. J. J., aged 26, of asthenic build, was admitted to the sick list on July 25, 1944, complaining of precordial pain and palpitation of six months' duration. The examination showed no cardiac enlargement, a systolic cardiac murmur audible over the entire precordial area, an inverted T_4 wave in the electrocardiogram, and an elevated blood sedimentation rate of 27 mm. per hour (Cutler). On October 4, 1944, the diagnosis of primary atypical pneumonia was made, owing to migrating areas of consolidation in the lungs. On October 13, 1944, the diagnosis of rheumatic fever was made because of the slight fever, persistent tachycardia, systolic cardiac murmur, mildly painful joints, evidence in the lungs of a rheumatic pneumonitis, and the elevated blood sedimentation rate. On June 2, 1945, the patient complained of increased precordial pain. The patient was placed on complete bed rest because of the persistent precordial pain, constantly changing pattern of the T waves in the electrocardiograms and the elevated blood sedimentation rates. With dramatic suddenness the precordial pain increased and death occurred abruptly 8 hours later (figures 3, 4, 5 and 6).

The gross pathologic examination showed marked cyanosis of the lips and nail-beds. The pericardium was not thickened and contained 20 c.c. of straw-colored fluid. The heart weighed 400 gm. The thickness of the right ventricle was 5 mm., the left

14 mm. The circumference of the tricuspid orifice was 11 cm. The tricuspid leaflets were thickened, but moved freely. The circumference of the mitral orifice was 8.5 cm. The mitral leaflets were thickened, but remained competent. The circumference of the aortic orifice was 6 cm., and the leaflets were greatly thickened. The base of the aorta in the region of the sinuses of Valsalva was greatly thickened and distorted. The left coronary artery was extremely narrowed by an atheromatous plaque a short distance from its origin. The descending branch of the left coronary artery appeared to be obliterated by a soft mass. The wall of the left ventricle showed areas of fibrosis suggesting old myocardial infarcts. The lungs were crepitant throughout. There was some congestion in the basal lobes. There were no areas of gross pulmonary infarction. The trachea and pulmonary arteries were patulous. There was a

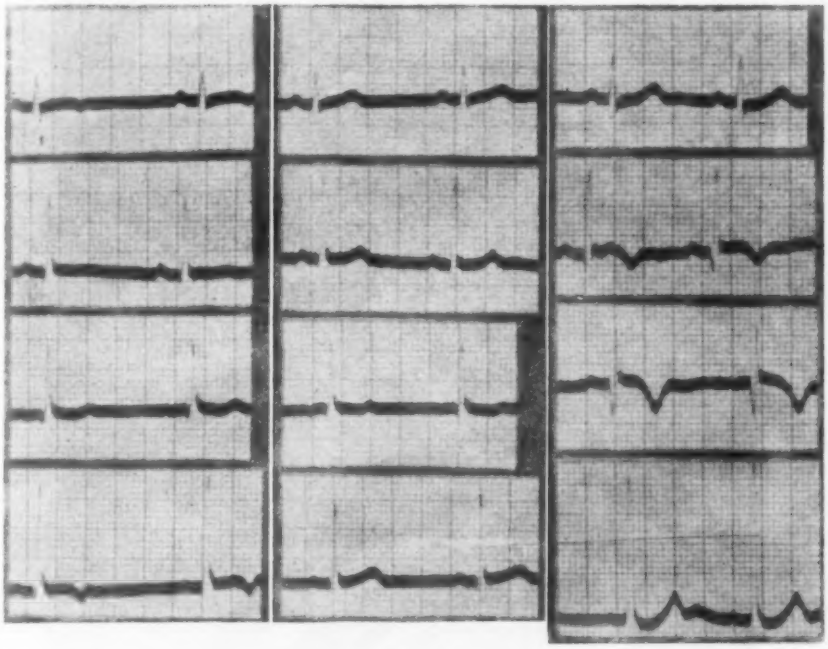

FIG. 4. FIG. 5. FIG. 6.

soft atheromatous mass in the left internal carotid artery at the point where it enters the Circle of Willis.

In the microscopic study the myocardium was thickly strewn with cellular aggregations which could hardly be called anything but Aschoff bodies. These were for the most part of the "polarized" variety. Many were distorted by fresh hemorrhage. Infarcts of various ages were conspicuous. Large and small coronary arteries showed changes which resembled those found in case 1, save that those in the large arteries were much more cellular. The mitral valve showed fibrinoid material, cellular vegetations, and accumulations of cells deep within the valve. There was conspicuous cellular infiltration and edema in the aortic valve and the base of the aorta, with a large amount of acidophilic "fibrinoid" material in adjacent tissue. The epicardium showed some fibrocytic reaction. In the lungs was periarterial and endoarterial fibrosis, with a few cellular endoarterial vegetations. There was marked proliferation of alveolar endothelium. The liver showed periportal accumulations of mononuclear cells. The material in the internal carotid artery was hyaline and acellular. Hyalinization was

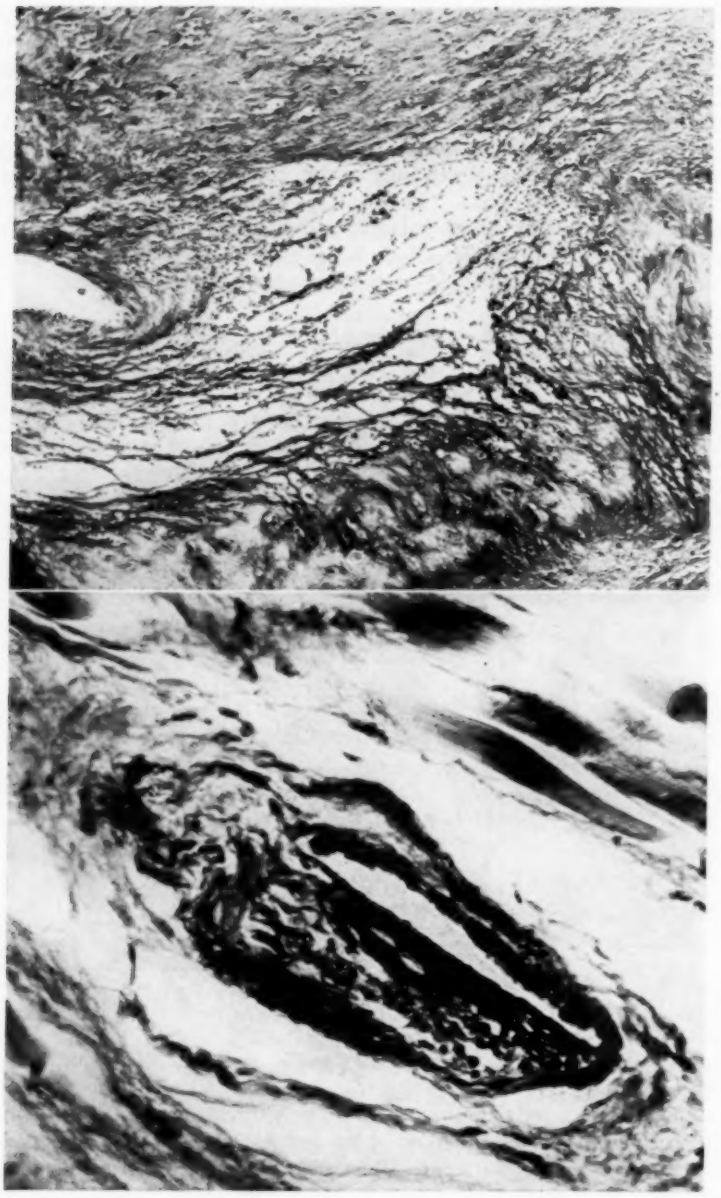

FIG. 7. (*above*) "Collagenous" mass in wall of coronary artery. Masson Trichrome stain, × 70.

FIG. 8. (*below*) Cellular reaction in and around small myocardial artery. Masson Trichrome stain, × 420.

conspicuous in the glomeruli and in smaller cerebral arteries. In the arachnoid were periarterial cell groups resembling Aschoff bodies.

Anatomical Diagnosis: Acute and subacute rheumatic arteritis and pancarditis; myocardial infarction (figures 7 to 13).

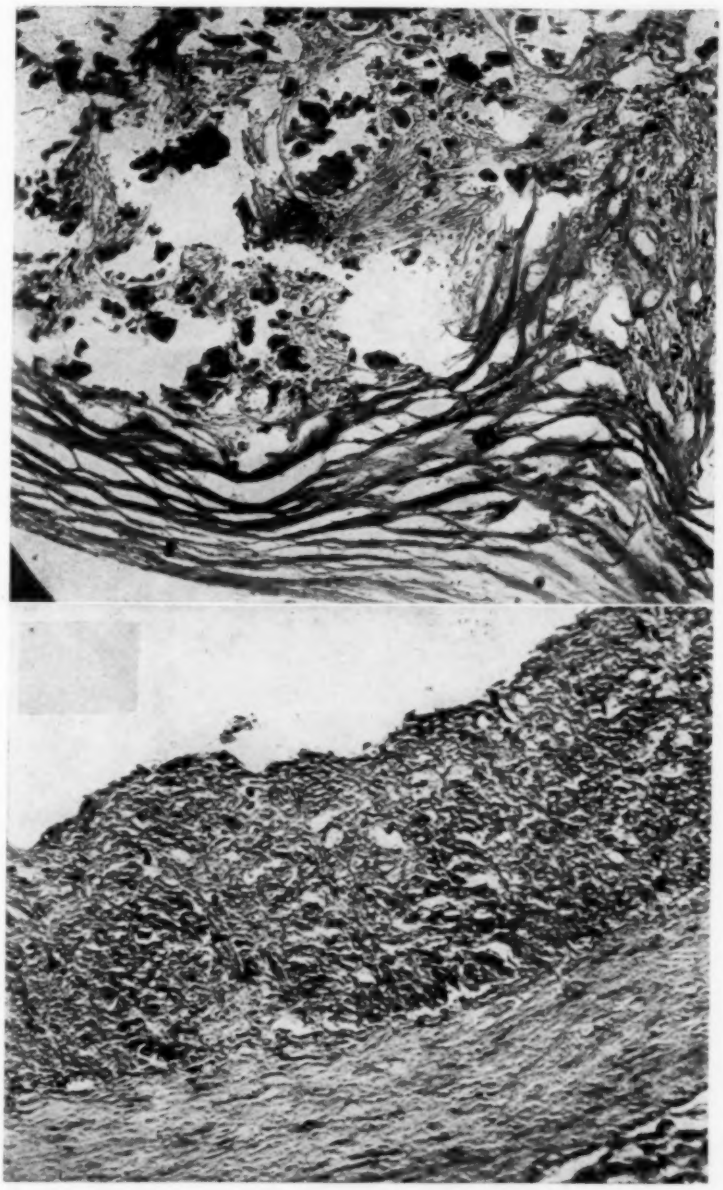

FIG. 9. (*above*) Calcification at base of aortic valve. Van Giesson stain, × 70.
FIG. 10. (*below*) Coronary artery showing mural edema. Van Giesson stain, × 125.

DISCUSSION

Perhaps the most striking common feature in these three cases is the occurrence of distinctive lesions at the base of the aorta. In cases 1 and 3 there was unequivocal histologic evidence of widespread vascular disease,

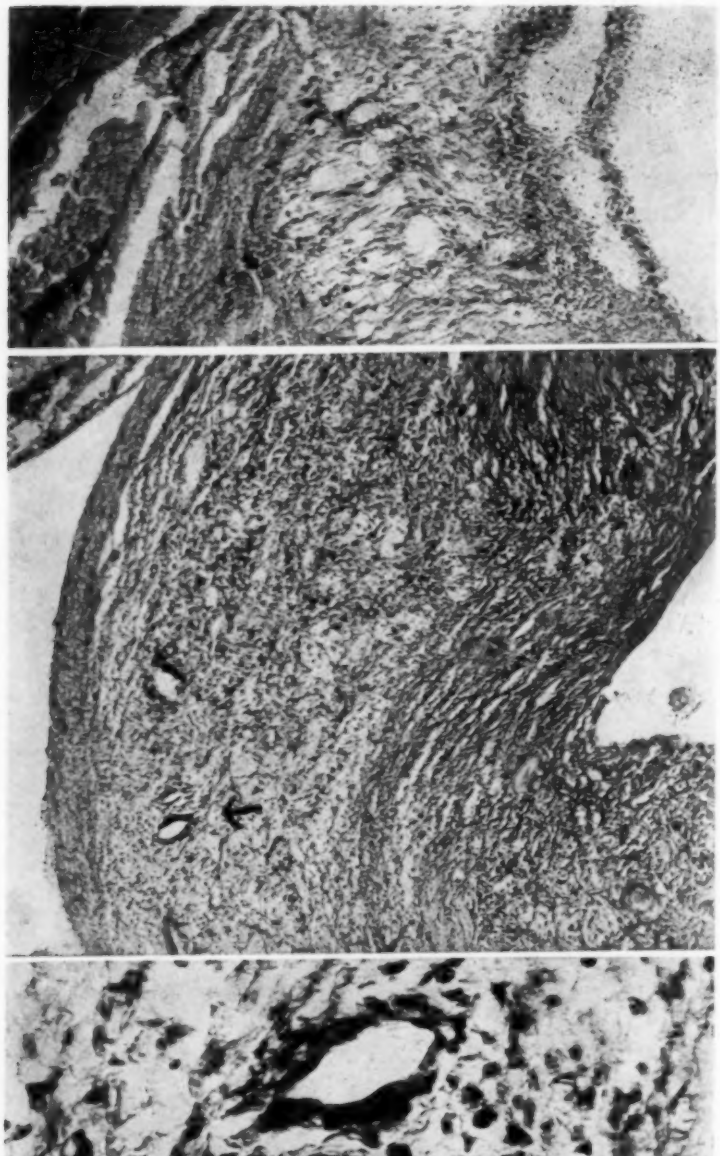

FIG. 11. (*above*) Infarcted area showing necrosis of heart muscle and edema and cellular infiltration of endocardium. Van Giesson stain, × 90.

FIG. 12. (*center*) Coronary artery showing extreme fibrosis, cellular accumulation and vascularization. Van Giesson stain, × 90.

FIG. 13. (*below*) Higher magnification of area in figure 12 marked by arrow.

particularly in the coronary and pulmonic circuits. The age of these changes cannot be determined by histologic examination. That much of the alteration in the coronary arteries was relatively acute is suggested by the clinical and electrocardiographic histories. In case 3 it seemed probable that the pulmonary vascular changes were related to the episode of "atypical pneumonia." If analogies suggested by recent pathologic and experimental observations are justified, then accumulation of relatively homogeneous acellular material ("hyaline," "swollen collagen" or "fibrinoid") might be considered as a very early histologic manifestation of acute vascular damage. Such a guess would suggest that the coronary disease was more recent in case 1 than in case 3. This suggestion seems corroborated by the absence of histologic evidence of infarction in case 1, and by the clinical and cardiographic records. If the extreme narrowing of coronary lumina in case 1 is as recent as the data suggest, one would, of course, assume that tissue particularly liable to acute swelling had been laid down some time in advance. The pulmonary artery changes in this case seem older than those in the coronaries. The history in case 2 strongly suggests a "stroke" referable to the coronary arteries, and the histologic findings are quite compatible with this notion. However, though the arterial edema is focal, and like that seen in other cases, it is possible that these changes are in part artefact due to submersion. Satisfactory interpretation is therefore difficult.

The question of the justifiability of the rheumatic diagnosis in these cases has been discussed at length elsewhere. It is difficult to see how the valvular changes in case 2 and the myocardial cell groups in case 3 could be called anything else, and in general we think the assumption that arterial and endocardial changes have nothing in common is probably an unreasonable one. The question of whether arterial changes in such cases should be termed rheumatic seems largely a matter of definition, in which the reader is entitled to his own view.

On histologic grounds one could not distinguish between these arteries and those which in the aged would readily be termed sclerotic. It would be imprudent to maintain that the mechanism of acute coronary death in these young individuals with a clinical diagnosis of rheumatic fever or rheumatic heart disease was essentially different from that in older individuals without such a diagnosis. Many of the obvious clinical phenomena in myocardial infarction seem to suggest an acute change rather than an insidiously progressive one, and there seems no reason why the aged should not suffer from acute coronary arteritis. However, in these cases the youth of the patients and the clinical data strongly suggest that the vascular changes are actually acute.

Summary

1. From a total of 13 deaths attributable to rheumatic fever which occurred in a series of rheumatic fever patients observed for a period of 18 months, three deaths were sudden, unexpected and dramatic.

2. In one case rheumatic cardio-angiitis was diagnosed clinically.

3. Gross and histologic studies of the pathological material showed unquestionable evidence of rheumatic fever.

4. The cause of abrupt death in each of the three cases appears to be an acute anaphylactic coronary angiitis superimposed upon a low-grade rheumatic carditis.

Photomicrographs by Mr. Edward N. Hamilton, College of Medical Evangelists, Los Angeles.

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THE MALARIA TRIAD *

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PERIODIC chills with fever,[1, 2, 3] splenomegaly,[4, 5] and anemia [6] have been traditionally recognized and taught [7, 8, 9] as the diagnostic triad of malaria. Even the most recent publications continue to propagate this dictum.[10] Boyd,[11] in 1944, states categorically: "Clinically active malaria infections, regardless of the species of their causative parasite, exhibit three basic symptoms: (a) fever, (b) anemia, (c) splenomegaly."

Recent experience with acute malaria cases, however, leads one to believe that the value of the triad in diagnosis of this disease deserves much reconsideration. True, a patient with typical periodic fever, splenomegaly, and anemia is more than likely harboring plasmodium parasites. But, for a clinician's diagnosis to depend on the appearance of these signs is like waiting for acidosis or coma to diagnose diabetes.

A series of 143 acute malaria cases, proved by blood films, was admitted to a Naval Hospital in Panama between November 15, 1943 and September 1, 1945. The occurrence of the malaria triad in these cases is summarized in chart 1. The group is considered representative in that it includes in-

CHART I

Symptoms	Patients	%
1. Periodic chills and fever (typical) (a)	9	6.34
Patients with chills and fever (atypical)	81	
Patients with chills	2	
Patients with "chilliness"	11	
Patients with fever	47	
Patients with fever (typical)	5	
2. Palpable spleen	47	33.0
3. Anemia (b)	23	24.7
Erythrocyte count below 3,500,000	3	
Erythrocyte count below 3,000,000	2	
Hemoglobin below 14 grams	15	
Hemoglobin below 13 grams	8	

(a) The terms typical and atypical refer to tertian or quartan cycles. It is well known that falciparum fevers are frequently not cyclic.
(b) Complete blood studies are recorded in only 93 cases and the percentage figure is on that basis.

fections by all three types of plasmodia as follows: *Plasmodium vivax:* 96; *Plasmodium falciparum:* 42; *Plasmodium malariae:* 3; Mixed *Falciparum* and *Vivax:* 1; *Unclassified:* 1. Of these 143 patients, 103 were suffering with their first attack of malaria, whereas in 40 the infection was recurrent.

The small number of cases with anemia is even more significant when it is appreciated that erythrocyte counts and hemoglobin values are generally reduced in the tropics. In 1000 consecutive male admissions to this hospital

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for all reasons the average erythrocyte count was 4,438,000 and the hemoglobin value, 13.7 gm. As Manson-Bahr [12] says: "Pale faces become still paler in the tropics and the condition is likely to progress there."

Numerically, this series is not large. However, our findings in this study closely correlate with observations of others on greater numbers of cases in various parts of the world. This is summarized in chart 2.

Further condemnation of the triad as a means of early diagnosis of malaria is expressed by Talbot,[20] and Most and Meleney.[21] Talbot states:

CHART II

Author	Noehren	Geneway[13]	MacDonald[13]	Simpson et al.[14]	Kean and Smith[15]	Gordon et al.[16]	Applebaum and Shrager[17]	Hughes and Bomford[18]	Clark[19]	Clark[19]
Location	Panama	China	India and West Africa	South Pacific	Panama	South Pacific	Panama		West Indies	West Indies
No. of patients	143			1184	100	435	125	854	2585	462
Characteristic chills and fever	6.34%				49%	80%				
Characteristic fever	3.5%							57.2%		
Palpable spleen	33%	24%	50%	17.3%	30%	23%	11.2%	36.8%	4.2%	38%
Anemia: Less than 3.5 million RBC	3%			7.5%		2.4%				
Less than 3.0 million RBC	2%			4.9%						
Less than 14 grams Hgb	16.1%					26%				
Less than 13 grams Hgb	8.6%					3%				

"We especially had to give up the idea that chills and periodic fevers were constant symptoms of malaria. . . . Cases go undiagnosed because they are never characterized by chills or fever or any textbook course of malaria." Most and Meleney, in discussing *P. falciparum* infections warn that waiting for the triad is dangerous because it does not always exist. They cite a tragic example of such a delay.

Kean and Smith [15] in analyzing 100 deaths from *P. falciparum* infection state: "No particular conclusions could be drawn from a study of the temperature charts. Some patients had high fever, others had little elevation of temperature." Fitz-Hugh et al.[22] also found that a few of their cases were "practically afebrile."

Lack of anemia, even in cases with numerous recurrences was noted by Metcalf and Ungar [28]: "Total counts in 102 patients gave an average of 4.1 million per cu. mm. Only 3 cases dropped below 3 million. Hemoglobin determinations in 44 instances paralleled the erythrocyte level closely, with an average color index of 0.93. Morphologically the red blood cells showed no significant departure from normal. In general, the size, shape, and color of the erythrocytes in these cases did not show remarkable variations."

Absence of splenomegaly has been also observed for some time. Deaderick [24] in 1909, commented: "The value of the enlargement of the spleen in the diagnosis of malaria has certainly been overrated." In the same year Craig [25] also stated: "While there can be no doubt that the organ is enlarged the enlargement in many cases is not demonstrable and a very large proportion of cases do not present a palpable spleen."

Further lack of splenomegaly was noted by Kern and Norris,[26] in studying liver enlargement in 1153 veterans returning from the Pacific with malaria. They observed: "Enlargement of the liver, like that of the spleen, seemed to follow the course of the disease. It was not palpable at the onset of the disease but enlarged during the first days of the fever." A careful study of the course of splenic enlargement was made by Stratman-Thomas.[27] He found, "the degree of splenic enlargement attained is directly proportional to the duration of the clinical attack. Attacks of ten days' duration or less tend to promote palpability only on deep inspiration with the maximum enlargement noted at the end of the second week. This enlargement disappears during the third week after the clinical attack." Hunt,[28] after extensive experience with the disease in North Africa feels: "To wait for a positive smear or a palpable spleen costs more lives than to treat a suspected patient." Barber and Rice [29] found splenic enlargement "a useful but not very accurate measure of the amount and distribution of malaria in Egypt."

Strong [13] summarizes the situation as follows: "While there has been considerable difference of opinion from time to time about splenic index in the diagnosis of malaria, palpability of the spleen, temperature curves and cyclic manifestations should not generally be considered by the practitioner reliable for the diagnosis without microscopical examination." We fully agree with Strong's statement and might add that it is dangerous to wait for these signs before doing a microscopical examination of the blood.[30]

An explanation of this change in significance of the malaria triad is not difficult to find. One of the fundamentals underlying the progress of medicine in recent decades has been earlier recognition and diagnosis of disease. No longer must a mass be palpable in the abdomen to suggest cancer of the stomach. Neither must a patient be jaundiced to diagnose liver disease.

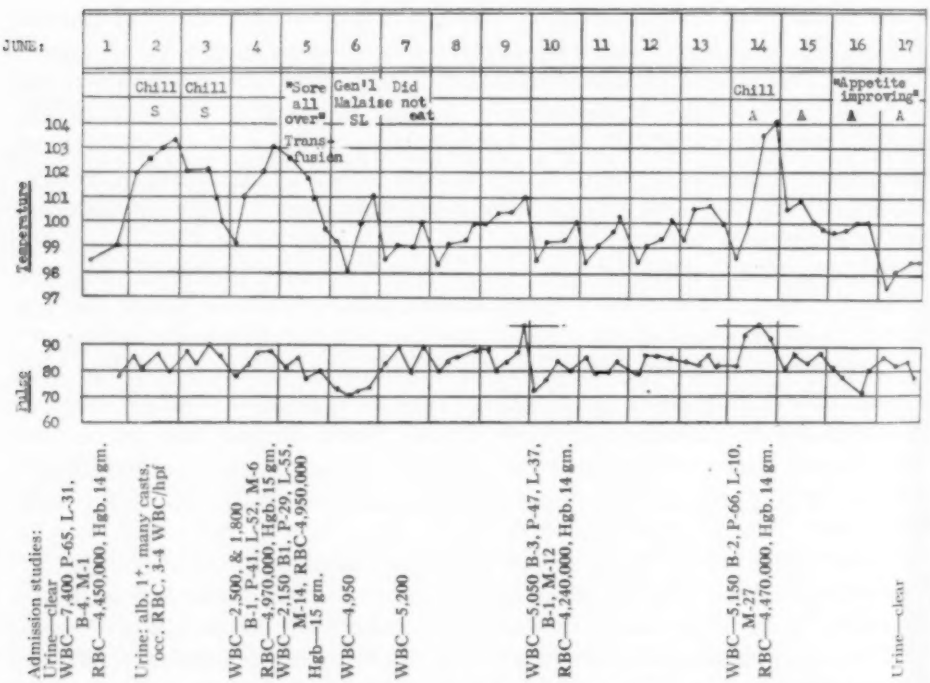
The same is becoming true of malaria. Patients, especially military personnel, are accessible to medical observation before the signs of established infection have developed. In our group of malaria cases (except for eight patients whose history exceeded 21 days), the average duration of complaints before admission was only 4.4 days. Many were seen in the first hours of

discomfort. The complaints, then, as we saw them, were really what textbooks have long called the "prodromal signs" [31, 32] of malaria. The triad of periodic chills with fever, anemia, and splenomegaly, is a later manifestation of an established plasmodium infection. Its clinical value must be reconsidered in that light, for the diagnosis of acute malaria is now made before that triad develops.

The temporal relationship of malaria symptoms and signs was fairly well demonstrated by patients in this group who developed clinical malaria while hospitalized for unrelated conditions:

A 34 yr. white F2/c was admitted to the surgical service on May 4, 1944, with the diagnosis: "Dislocation, right shoulder." No temperature or systemic complaints were noted for the first 16 days, after which a Nicola operation was performed on his shoulder. For seven days post-operatively he had an afternoon elevation of temperature never exceeding 100° F. The next five days were completely afebrile. On his thirtieth hospital day he had a chill rather suddenly and a fever of 103.4° F. His clinical course from that time on is charted below (chart 3). Blood films for malaria

CHART III



(S—sulfadiazine therapy (total–7 gm.), SL—serious list; A—atabrine therapy)

were examined repeatedly for three days, June 3 to 6. All were negative for malaria parasites. The spleen was never palpable. June 14 he had another chill and rise of temperature to 104° F. At that time *Plasmodium vivax* was found. A routine course of atabrine (total 2.6 gm.) resulted in an uneventful recovery. He was discharged asymptomatic on July 31, 1944. No history of previous malaria infection was obtained on requestioning the patient.

A similar episode occurred in a 19 yr. white SM 3/c from whom a suppurative appendix was removed on July 4, 1944. He ran a low-grade postoperative fever for 10 days, after which he was afebrile for eight days. The following day he noted "malaise, headache," and a temperature of 102° F. This continued for five days, with urinary and blood findings almost identical to those of the other case. At this time he was starting to show the tertian fever cycle, and his blood was found to contain *Plasmodium vivax*. Atabrine in the usual dosage produced an uneventful recovery. There was no history of previous malaria infection. Following three days of sulfadiazine therapy this patient also showed agranulocytosis (white blood cells 3000, with 4 band, 9 segmented, 71 lymphocytes, 1 eosinophile, and 15 monocytes). The sulfadiazine may [33] or may not [34, 35] have affected somewhat the course of the infection, but the sequence of symptoms and signs was fairly typical. It is a reasonable assumption, on the basis of other acute cases seen here, that the triad may have become apparent later in each case if atabrine had not been started.

Failure to recognize the "prodromal" complaints as of malarial origin has caused numerous diagnostic errors, some of which have been tragic and fatal.[36] Kean and Smith [15] found that in 100 fatal cases of estivo-autumnal malaria, 23 had symptoms of not more than one day before hospitalization, and yet they died. Even in Panama, where, in the minds of many, malaria is practically synonymous with the region, less than 72 per cent of our malaria patients were hospitalized with suspicion of the correct diagnosis, and only 28.5 per cent admitted with the correct diagnosis established.[37]

These errors would be less significant if it were not true that the early complaints in malaria cases possess rather consistent similarities. The pattern, as seen in our group, was characteristic enough so that even the ward corpsmen could make a fairly accurate diagnosis before the blood film report was available.

Six complaints have been found most helpful: fever, headache, malaise, backache, anorexia, and "foul smelling" perspiration. The diagnosis of malaria was established in a significant number of patients who manifested any four of these six complaints.

Fever has always been suggestive of malaria, especially when associated with chills. It is not always present, however, much less so in its typical cyclic form, as has already been mentioned. Fever was noted in 96.7 per cent of our group; in 63.4 per cent associated with chills. No appreciable fever was present in 12 patients on admission.

Headache was a symptom in 73 per cent of our patients with malaria. From more careful questioning of recent cases it is apparent that this percentage would be higher if the various admitting examiners had asked specifically for this complaint. The headache is characteristically, though not always, frontal or retrobulbar, with common reference to it as a "tired" or "strained" feeling in the eyes.

Malaise is a common complaint in many diseases. It assumes an identifying place in malaria for its sudden and unexplainable onset. It frequently is the first sign in a man who is perfectly all right until this sudden "ache

all over," "tired," or "dragged out" feeling seizes him. This was seen in 71 per cent of our cases, and in 40 per cent was mentioned as the chief complaint.

Backache was complained of by 32.4 per cent of our patients. In all probability it was included even more often under the symptom of malaise. It is characteristically in the lumbo-sacral area, and occasionally severe enough to require morphine.

Anorexia was a prominent complaint in 44 per cent of our cases; associated with vomiting in 9.2 per cent. As additional diagnostic evidence it is valuable. Rarely has a good appetite been seen in a man acutely ill from malaria. In the course of treatment the disappearance of anorexia is a valuable indication of the clearing of these parasites from the blood. Persistence of anorexia is highly suggestive that the treatment has been inadequate and further study of blood smears, especially for gametocytes, should be made.

Foul perspiration has a peculiar sour odor described by patients as like the smell of "burned matches," "phosphorus or sulfur." This symptom was first pointed out by a native of Panama who had experienced malaria paroxysms several times. It has since proved of some diagnostic value. Although noted in only 26.6 per cent of our cases, it was identified by them as something unusual. When present it was quite an accurate indication of a positive blood film.

Other observers have noted the above complaints with similar frequency. Gordon et al.[16] found them in the following percentage in their group of 435 soldiers evacuated from the Southwest Pacific: Malaise, weakness, 97 per cent; headache, 96 per cent; generalized aches, 88 per cent; backache, 88 per cent; nausea, 59 per cent; vomiting, 36 per cent. Hughes [18] reports that in 1200 cases in West Africa, "the main symptoms of the attack irrespective of type and in order of frequency were: headache, backache, shivering, vomiting, feverishness, pain in the back of the neck, generalized aching, slight cough, sweating, and simple diarrhea."

Craig [25] in 1909 wrote: "In all cases of malaria there is loss of appetite, often observable for days before the onset of the febrile paroxysm. . . . Headache occurs in practically every case. . . . Pain in back and limbs is always present during acute attacks of malaria and may be very severe." Bercovitz [31] says: "In most instances, for a few days before the occurrence of the actual malarial paroxysm the patient complains of aching bones and joints, pain in the back and legs, more or less malaise, anorexia, headache, etc."

Polumorovinov [38] and Troitzky,[39] reporting the deaths of 34 children in Russia, observed: "The children who succumbed showed no constitutional anomalies, the main subjective symptom being severe headache." Fitz-Hugh et al.[22] studied 189 cerebral malaria cases and found that: "In all in whom an adequate history was obtainable, headache was severe. Photophobia and vertigo were frequent complaints."

Although these symptoms have occurred with significant frequency, they are not proposed as being diagnostic for malaria but only as highly suggestive of the disease. A great deal has been written lately of the bizarre symptoms of malaria. In fact, malaria has quite indisputably joined syphilis as another great medical "mimic," [40] simulating as it does, almost every known disease of the body.

A few of the other findings frequently mentioned in malaria are: upper respiratory changes,[41] hepatomegaly, elevated sedimentation rates, leukopenia, urinary changes, false positive serologic reactions,[42] bradycardia,[18] jaundice, herpes, and cerebral manifestations.[43]

In our cases 23.6 per cent had upper respiratory complaints or findings. In fact 13.6 per cent were admitted with a diagnosis of an upper respiratory or catarrhal fever. Hepatomegaly was noted in 11.9 per cent. Of the sedimentation rates examined on admission (24) only 30 per cent were elevated, which is contrary to the experience of Wood [44] who found 84 per cent elevations. Leukopenia (under 5000) was present in 19 per cent on admission, and leukocytosis (over 10000) in 4.2 per cent. Urinary changes consisting of varying degrees of albuminuria, casts, erythrocytes and leukocytes were seen in 19.7 per cent of the cases. These changes cleared with the treatment of the malaria.

Of the Kahn tests made on all the malaria patients the day after admission, only 5, or 3.3 per cent were positive. This is essentially in agreement with what Bates [45] has found on admission serologic tests. The fact that the blood was drawn on admission rather than in the later days of the disease may explain the variance with reported figures of 9.9 to 80 per cent,[46] 100 per cent,[47] 47.5 per cent,[48] and 12.5 per cent [42] false positive reactions.

Bradycardia was frequently a helpful sign. In a new patient with a high fever, the presence of a pulse rate considerably less than the expected 10 points acceleration for each degree of temperature elevation (as seen in fevers of bacterial infection) strongly suggested malaria. Jaundice was present in one case. Herpetic sores were seen occasionally. Cerebral manifestations were seen in one man who was admitted with ataxia and difficulty in speaking.

This series of malaria patients has been reviewed in an attempt to show some consistency in symptoms in spite of the protean nature of the disease. To depend, however, entirely on these "consistencies" would be as fallacious as waiting for the ague-splenomegaly-anemia triad, but like the triad, they should be strongly suggestive. The diagnosis then rests on a blood film examination.

The failure to consider malaria and to do a usually simple blood film examination has been the source of most serious difficulties. Craig [49] feels, "If there is one fact that experience has proved in the realm of diagnosis, it is that without a blood examination one can never be sure of the diagnosis of malaria and hundreds, and the writer believes, thousands of lives have been sacrificed because of the neglect of this procedure by the practicing physi-

cian." It might also be emphasized here that a single negative smear does not rule out malaria. Frequently several thick and thin films, taken at various intervals, must be examined carefully before final diagnosis is made.[30]

The significance in all this may not be apparent to the practicing physician in civilian life, especially those in temperate climates, although they are aware that malaria has become *the* disease of World War II. They also realize that a few of the thousands of recurrent malaria cases among military personnel [50] may be in their hands in the next years. But all do not appreciate that *new* cases are also imminent.

The recurrent cases are often the easiest to diagnose. The patient himself recognizes the "feel" of malaria, an invaluable and reliable assistance in diagnosis. It must, however, be differentiated from the recently described "psychogenic malaria." [51]

With these recurrent cases at home, new infections are very likely to appear. Conditions in most of the United States, even in the most temperate areas, are as suitable today for the propagation of malaria as they were a century and less ago when the disease was common. There is ample evidence of the malariousness of the country in the pioneer period of the late eighteenth and nineteenth centuries. Not only the old malarious colonies of the East Coast, but all the new states with a more northern location, Indiana, Michigan, western New York, Kansas, Oklahoma, Missouri, Minnesota, Wisconsin, Illinois, and Iowa, all shook with the "ague." [52]

In New York City during the six years ending in 1890, the statistics show 2,060 deaths or 24.62 per 100,000 from malaria. In Baltimore there were 834 deaths or 41.51 per 100,000, and in Brooklyn 1,413 deaths or 32.62 per 100,000. Although the accuracy of these figures has been justifiably doubted by Thayer,[53] it is known that in the first half of the nineteenth century New York and Philadelphia and their environs were intensely malarious.

Packard [54] records the wide prevalence in places as far north as Madison Barracks, N. Y., Fort Winnebago, Wisc., and Fort Mackanaw, Michigan, and throughout the length and breadth of the Mississippi.

Christian [55] speaks of malaria in New England where it prevailed "extensively." It has been said that families in the Connecticut Valley had quinine on the dinner table, to be sprinkled on food like sugar, to prevent the "ague." Longfellow, referring to malaria, spoke a familiar warning in *Evangeline*: [56]

> Only beware of the fever, my friends, beware of the fever!
> For it is not like that of your old Arcadian climate,
> Cured by wearing a spider around one's neck in a nutshell.

Ackerknecht [52] says malaria was so prevalent that it was *the* American disease during the nineteenth century. He cites one of the most striking experiences, that of a French traveler, Comte de Volney. On a 700 mile trip from Cincinnati to Detroit in September 1796, he did not find 20 homes which were free of malaria.

It is felt [57] that there is little imminent danger of any serious epidemic of malaria in the United States at present. However, the conditions for transmitting the disease are still present, as is illustrated by a small epidemic which occurred in 1928 in Flint, Michigan. It was the result of southern workers who were carriers of the infection coming to work in automobile factories. In recent years there have also been outbreaks in southern Minnesota, eastern Iowa, northern Ohio, and in Camden, N. J. In the summer of 1943 an outbreak of 53 cases occurred in a small town in Illinois.[58]

Malaria has thus become an important subject for all medical men, military and otherwise. The triad of periodic chills with fever, anemia, and splenomegaly as a diagnostic criterion, should be seriously reconsidered by everyone concerned.

Summary

1. Periodic chills with fever, anemia, and splenomegaly have been traditionally recognized and taught as the triad of malaria. Recent experience with acute cases indicates this triad no longer constitutes the key to diagnosis.

2. So-called "prodromal" complaints are sufficiently consistent to suggest the diagnosis at earlier stages of the disease. These include fever, headache, malaise, backache, and "foul-smelling" perspiration.

3. The final diagnosis still rests on finding the parasite in a blood film. Failure to consider the disease and this usually simple means of diagnosis has resulted in many errors, some fatal.

4. Conditions for ready propagation of the disease from returning military personnel prevail in most parts of the United States, even in the northern states where malaria was once endemic. The situation promises to affect many clinicians to whom malaria is an unfamiliar disease, remembered primarily for its triad of periodic chills with fever, anemia, and splenomegaly.

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THE MEDICAL MAN AND THE CONSTITUTION *

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MEDICAL STANDARDS

LICENSE REQUIRED

IN his opinion in Lambert v. Yellowley [1] Mr. Justice Brandeis uttered the following dictum: "Besides, there is no right to practice medicine which is not subordinate to the police power [2] of the states. . . ."

One decision cited by Mr. Justice Brandeis to support his dictum was Dent v. West Virginia.[3] That state in 1882 passed a statute which required every medical practitioner to meet one of three standards: (1) a graduate of a reputable medical college; (2) a practitioner in West Virginia continuously for ten years prior to March 8, 1881; or (3) pass an examination prepared by the State Board of Health. Dr. Dent had only practiced since 1876. He had a diploma from the American Medical Eclectic College of Cincinnati, Ohio, but that college had been determined by the Board of Health not to be "reputable." Dr. Dent did not submit himself to the examination of the board. He was convicted for violating the West Virginia statute. The Supreme Court of the United States affirmed the conviction and thus determined that the statute was no violation of due process guaranteed by the Fourteenth Amendment. There are many similar decisions.[4]

LICENSE REVOCABLE

Licenses to practice medicine may be revoked by a state board. The courts generally have refused to hold that statutes conferring this power violate constitutional provisions. The usual claim has been that due process was denied. More particularly it has been argued that statutes permitting revocation were unconstitutional because the grounds for revocation were stated in general terms, such as gross immorality or unprofessional conduct. Most courts have not been convinced by this argument.[5] Some of them, however, have held that such grounds are so vague as not to give fair notice. Such a defect, according to the minority view, makes a revocation of license statute unconstitutional.[6]

DISCRIMINATION

Statutes regulating members of the several professions practising the healing arts do not have to treat each profession precisely the same. The test, when complaint is made that the statutes deny equal protection of the

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laws (class legislation), is whether the discrimination is plainly unreasonable.[7] Louisiana discriminated against chiropractors by requiring them to pass satisfactory examinations in the same subjects that were specified for physicians and surgeons, including surgery and materia medica. Other statutes provided for the admission of osteopaths, dentists, chiropodists, and trained nurses without requiring them to take a full course in materia medica or surgery. In other words, the osteopaths were favored and the chiropractors were, it would appear, practically prevented from practising in Louisiana. But this patent discrimination was sustained by the Louisiana Supreme Court.[8] It stated: "Were it otherwise the legislature would be greatly hampered in the exercise of its power to protect the general health and the public from imposition and fraud. Every group of men who might get together and evolve some system, designed to restore health, would be entitled to recognition, and all that could be required of them would be evidence of good character and a knowledge of such subjects as their particular school seemed to require, although the legislature might deem with reason a knowledge of such subjects wholly insufficient to entitle any one to treat the sick." This reasoning by the Louisiana Supreme Court does not appeal to this writer as a perfect example of logic. The states should have the power to deny recognition to schools of medicine that are not valuable to society.[9] That fundamental proposition would hardly be denied by any disinterested person. But should a state be permitted to require standards for chiropractors in excess of those for osteopaths? However, even if the answer to this question must be in the negative, it would not necessarily follow that Louisiana could not properly deny admission to chiropractors. Conceivably its board might have reasonably determined that the chiropractors failed to present "a diploma from a college in good standing." Perhaps there was at that time no such college teaching the system known as chiropractic.

Probably it is not of much importance now, but in establishing a standard of education as a condition to securing a license, it is no violation of equal protection to make a reasonable exception in favor of established practitioners.[10] The Minnesota legislature in 1919 revised its statutes concerning the practice of dentistry. Section four of this revision authorized the board of dental examiners to suspend or revoke dental licenses for a number of specified reasons. Section eight had a sweeping provision in this language: "provided that the provisions of this act shall not apply to persons lawfully engaged in the business or practices of dentistry at the present time." It is a fair guess that the legislature intended merely to permit dentists licensed before 1919 to continue to practice without qualifying again for a new license. But the Minnesota Supreme Court held that section eight plainly excluded these dentists from the disciplinary provisions of section four. This discrimination was a violation of constitutional provisions for equality and thus made the revision invalid.[11]

In a Florida case, T. K. Jones stated that he had taken three examina-

tions given by the Florida State Board of Dental Examiners; that he had been thrice notified that he had failed to pass; but that he had made as high a mark as others who were granted certificates to practice by the Board. Accordingly, Jones claimed that he had been refused a certificate capriciously and from prejudice. After the board's motion to quash the proceedings had been overruled, the board declined to give any further answer to Jones' complaint. Thus the actual facts were not adequately developed. But on the meager showing it would appear that the Florida court acted correctly in compelling the board either to justify its conduct or to issue a certificate to him. To do otherwise would seem to violate the constitutional guaranty of equal protection; but this provision was not mentioned by the Florida Supreme Court.[12]

Advertising

Oregon passed a statute that placed severe limitations upon the advertising permitted by dentists. The Supreme Court of the United States held that the statute was valid, saying: (1) "Nor has plaintiff any ground for objection because the particular regulation is limited to dentists and is not extended to other professional classes. The state was not bound to deal alike with all these classes, or to strike at all evils at the same time or in the same way. It could deal with the different professions according to the needs of the public in relation to each;" and (2) that defendant was not justified in advertising in the forbidden manner merely because his advertisement was truthful. The court also observed: "The legislature was not dealing with traders in commodities, but with the vital interest of public health, and with a profession treating bodily ills and demanding different standards of conduct from those which are traditional in the competition of the market place. . . . And the community is concerned in providing safeguards not only against deception, but against practices which would tend to demoralize the profession by forcing its members into an unseemly rivalry which would enlarge the opportunities of the least scrupulous. What is generally called the 'ethics' of the profession is but the consensus of expert opinion as to the necessity of such standards." [13]

Corporate Practice

Despite a dissenting minority, it has been generally agreed by the courts that neither a corporation for profit nor any other unlicensed person may practise medicine, surgery, or dentistry through licensed employees. Such a policy by a state does not offend constitutional provisions.[14]

Apparently in no state have private corporations for profit made more determined efforts to practice medicine and dentistry than in California. They were denied this right when the effort was directly attempted. Then they made an indirect effort as disclosed by the opinions in People ex rel. State M. Exrs. v. Pacific Health Corp.[15] This corporation for a premium

agreed to pay the policy holder for medical services rendered to him; but to obtain this benefit the holder "must, save as to emergency expenses not exceeding $50, accept a doctor from the list" of physicians and surgeons approved by the corporation. This restrictive provision appears to be the main point of difference between this corporation and other insurance companies which issue the long accepted ordinary health and accident policy. The defendant, Pacific Health Corporation, was operating for profit and was seeking to make as many of its contracts as possible. But the Supreme Court of California held that it was illegally engaged in the practice of medicine in excess of its corporate powers. The court refused to heed the argument made by the corporation that the doctors on its approved list were independent contractors as opposed to employees in other cases where corporations were found to be practising medicine. This was rejected as a technical distinction and the court reasoned thus: "The evils of divided loyalty and impaired confidence would seem to be equally present whether the doctor received benefits from the corporation in the form of salary or fees. And freedom of choice is destroyed, and the elements of solicitation of medical business and lay control of the profession are present whenever the corporation seeks such business from the general public and turns it over to a special group of doctors." To answer objections made by the three judges who dissented, that the decision would be a peril to "fraternal, employee, and hospital associations and various medical-hospital services [that] have been rendering such services to their members through doctors employed by them" and also to health insurance and group medicine, the majority of the court was happy to say: "It is perfectly possible to bring adequate medical service to the vast numbers of people who now can ill afford it by some means which will protect both the profession and the public from the evils of corporate control of the practitioner." Then the majority cited as an example of what it had in mind, Butterworth v. Boyd decided the same day. That case is discussed in the next paragraph.

In 1937 the city and county of San Francisco established a health service system for all of its employees who were members of the retirement system, including the teachers and employees of the board of education. The system was to be administered by a board to be elected by the members of the system. Members of religious sects who believed in healing by prayer were exempted from the system at their option. The board had the power to exempt those whose annual salaries exceeded $4,500, and those who had otherwise provided for adequate medical care. The board had the power to adopt (1) a plan for medical care, (2) for indemnification of the costs of medical care, or (3) for carrying insurance against such costs. To pay the expense of the system the board could determine the monthly sum to be deducted from the compensation of the members. From the fund so obtained all expenses of the system were to be paid. Members in seeking medical care were free to select their physicians, nurses, hospitals, etc., subject to these restrictions only: (1) the rules and regulations of the board; (2) the chosen doctor or

hospital must render his services pursuant to these rules and regulations; and (3) the services or supplies must be furnished at uniform rates of compensation to be fixed by the board. But the board was expressly prohibited from entering into any exclusive contract for these services. The first board adopted plan number one for the rendition of medical services and rules and regulations to carry it into effect. A monthly deduction of $2.50 was made and then came a suit to test the constitutionality of the legislation. The Supreme Court of California, with one judge dissenting, decided that the legislation was valid despite many objections such as delegation of legislative power, due process, equal protection, and religious freedom.[16] It is hardly to be doubted that the court was happy to announce that the municipal employees had voted in favor of the system at the outset by a vote of 7,428 to 939 and that: "Over a thousand physicians, a majority of the licensed practitioners in the city, and nearly all of the city's hospitals, agree to furnish services under the plan. And petitioners' brief states that among those who have joined the staffs are the president of the State Board of Health, the president of the California State Medical Association and past presidents of that association, the president of the San Francisco County Medical Society and several past presidents of that society, the president of the American College of Physicians, and leading members of the staffs of the medical schools of the University of California and Stanford University." The uncertainty in this opinion is contained in the expression, "rules and regulations of the board." Until these rules and regulations are disclosed and discussed in a court opinion one cannot be sure of the scope of the opinion in Butterworth v. Boyd. But it would appear that the decision sustains the constitutionality of one type of group (socialized) medicine as distinguished from what may be labelled, inexactly, as the corporate practice of medicine.

A similar organization in California was known as California Physicians' Service, a non-profit corporation. The membership consisted of (1) administrative members who exercised administrative control through the election of the board of trustees; (2) professional members, duly licensed physicians and surgeons practicing in the state, who elected the administrative members periodically; and (3) beneficiary members, viz., those who upon the payment of monthly dues are entitled to secure from any professional member the necessary medical and surgical services. "Professional membership is open to any physician or surgeon licensed to practice his profession in this state upon his agreeing to abide by the rules of the corporation that all compensation for services rendered a beneficiary member shall be paid upon a pro rata basis out of the monthly funds collected from the beneficiary members." But a professional member could refuse to accept any person as a patient. It was stated by the corporation that approximately 5000 California physicians and surgeons were members and that 100,000 persons, increasing at the rate of 1500 per month, had become beneficiary members. Two years after the California Physicians' Service was incorporated, the California legislature passed an act applicable to the Service that

provided: (1) at least one fourth of all physicians and surgeons had to become members; (2) membership in such a non-profit corporation upon a uniform basis is available to all licensed members of a particular profession; and (3) voting by proxy and cumulative voting are prohibited. The California Physicians' Service was declared by the Court of Appeals, First District, to be validly operating under California laws and not to be engaging in the insurance business or in the corporate practice of medicine.[17] In the opinion of the court is the following language: "There is no essential difference between the Group Health Association, the San Francisco Health Service, and California Physicians' Service in so far as the scheme of operations is concerned except that in the first two the administrative management is in a board selected by the beneficiary members, whereas in the latter it is in a board selected by the professional members. All are non-profit, semi-charitable organizations conducted for the primary purpose of affording necessary medical care to those of small income."

The above expression "Group Health Association" refers to the opinions in Group Health Ass'n v. Moor and Jordan v. Group Health Ass'n. The first of these two cases decided that the Group Health Association, organized in the District of Columbia, was not practising the healing art or engaged in the business of insurance in violation of law.[18] The second case, in the Court of Appeals, affirmed this decision as to the second point only.[19] No appeal was taken from the decision on the first point. From the two opinions these facts appear concerning the Group Health Association. It was organized as a non-profit corporation to provide its members and their dependents with medical services, surgery, hospitalization and medical and surgical supplies. There were specified exceptions and limitations on the services. Membership was limited to civil employees of the executive branch of the United States government service. Members were elected by the boards of trustees, who in turn were elected by the members except two chosen by the Federal Home Loan Bank Board, all from the membership. Members paid monthly dues and they could be expelled by the trustees who controlled and managed the corporate affairs. The relationship between the corporation and the physicians was not very clear. It had discontinued its former practice of having a staff of full-time salaried physicians in favor of a system whereby the physicians under oral contracts "apparently devote only a portion of their time to the work of Group Health, the remainder being devoted to private practice, although it seems to be contemplated that some physicians will give full time to the work. They receive fixed annual compensation, paid in monthly instalments, not specific fees for each treatment or case." It operated a clinic and provided for home treatment, if necessary. Hospitalization to a limited extent was secured by arrangement with independent established hospitals. But it does not appear that Group Health provided that any licensed practitioner who would abide by the rules and regulations was entitled to be on the panel approved by Group Health for calling by its members. This absent feature seems to be highly important

under the California decisions. The Court of Appeals was apparently not concerned with this fact since its task was to decide whether Group Health was in the insurance business. The decision of the District Court that Group Health was not practising the healing art was expressed in a brief opinion that did not consider this possible objection. It was the conclusion of the Court of Appeals that doctors who made contracts with Group Health were "independent contractors" required to exercise their own judgment entirely independently as to diagnosis and treatment.

This is an appropriate place to ask what is the essential difference between the Group Health Association in the District of Columbia, the California Physicians' Service, and the San Francisco health service system on the one hand and the Pacific Health Corporation and the United Medical Service in Illinois on the other hand? The best answer appears to be the profit motive with its danger of divided loyalty, intellectual dishonesty, and shoddy medical service. This is a sufficient differentiation on paper. Yet it seems fair to observe that a non-profit association cannot be wholly immune to expense, to making ends meet, and administrative success. And these are factors that will hamper and probably prevent the attainment of the high ideal of entirely adequate medical service for those with low incomes. So it is feared that in practice there would not be a great difference between approved non-profit corporations and disapproved profit corporations if the latter had been generally permitted to develop. Some of the latter probably would have developed into institutions with good if not excellent records for service. It can hardly be doubted, however, that many of them would have been of poor quality and even disgraceful. Thus would have arisen a need for public supervision and that, in an approved fashion, is not easy to obtain or cheap. Accordingly, the final conclusion is that the non-profit coöperative way is the superior method. If that method proves to be successful there will be little or no regret that the "practice of medicine" by the profit corporation has been generally forbidden.[20]

Procedural Due Process

Not only is a physician entitled to substantive due process as set forth above, but he is entitled to procedural due process before his substantive rights can be adversely affected. Thus, the Ohio Supreme Court held that even though a statute provided that a license could not be revoked except upon notice and hearing, nevertheless it was unconstitutional because it failed to provide "whereby the attendance of witnesses could be required or their testimony procured." [21]

Missouri apparently was more careful than Ohio and provided by statute that testimony could be taken by deposition and used in the trial of a physician before the state board of health. Officers who take depositions were authorized to compel witnesses to attend and give their testimony. The Supreme Court of the United States held that this was sufficient for pro-

cedural due process even though the board had no power to compel witnesses to appear in person before the board and there give their testimony.[22]

Perhaps the most colossal quack to disgrace the American medical profession was John R. Brinkley, the goat gland surgeon, who barely missed election as governor of Kansas, even though he ran on an independent ticket —a remarkable feat that was equally remarkable proof of the emotional gullability of too many Americans. After the State Board of Medical Registration and Examination of Kansas filed a complaint to revoke his license, Dr. Brinkley sought to enjoin the board from holding a hearing because, among other complaints, the board lacked the subpoena power. He failed to obtain an injunction.[23] The Kansas Supreme Court said that: "With the exception of a sporadic case to be noted later, no court has ever declared that [an] opportunity to present [a] defense and be heard in its support requires the adjective element of compulsory process." The exceptional case mentioned by the Kansas court was the case decided by the Ohio Supreme Court. The Kansas Supreme Court was caustic in its adverse comment, viz.: "The decision is authority for nothing but the fact that it was rendered, and this court declines to follow it."

In 1930 the Kansas board revoked Brinkley's license. Then Brinkley sought to enjoin this revocation, claiming that it denied him his rights under the national constitution. He was unsuccessful but he confronted the federal courts with a difficult decision.[24] His best argument was that the members of the Kansas Medical Board were prejudiced against him before the hearing started and that some of them were active in making the complaint against him. The Circuit Court of Appeals admitted "that some of the board had expressed such prejudice, and doubtless all were in fact prejudiced." This conclusion was explained by the fact that Brinkley's methods of publicity, particularly the use of the radio, made previous knowledge of these facts and opinions concerning their violation of professional standards almost inevitable. Thus the court was confronted with a decision in favor of Brinkley, because the only body that could try him was disqualified by prejudice, or a decision adverse to Brinkley. In this unhappy dilemma the Circuit Court of Appeals chose not to let Brinkley go "Scot-free" and thus proclaimed that a doctor could not by sensational methods of publicity oust the only body with jurisdiction over him. And yet it is unfortunate for us to admit that a person had to be tried before a board that undoubtedly was prejudiced. Normally, courts could be expected to deny such a conclusion.[25]

It is implied in the preceding discussion concerning procedural due process that before adverse action is taken against a medical man, he is entitled to a notice and a hearing. So is the law written [26]; but it is also true that some courts have had an unfriendly attitude toward administrative tribunals and thus have been unnecessarily strict and legalistic in applying this sensible rule.[27]

Restraint of Trade

The American Medical Association and others were indicted for a conspiracy to restrain trade in violation of the Sherman Anti-trust Act. The Group Health Association of the District of Columbia was the alleged victim of the conspiracy. The District Court sustained demurrers to the indictment, holding that medical practice is not a trade within the meaning of Section three of the Sherman Act.[28] However, this decision was reversed and remanded by the Circuit Court of Appeals.[29] It held that "a restraint imposed upon the lawful practice of medicine—and a fortiori—upon the operation of hospitals and of a lawful organization for the financing of medical services to its members, is just as much in restraint of trade as if it were directed against any other occupation or employment or business." The opinion condensed the charge against the medical societies in this fashion: that they conspired to prevent the successful operation of Group Health's plan, and that the steps by which this was to be effectuated were as follows: "(1) to impose restraints on physicians affiliated with Group Health by threat of expulsion or actual expulsion from the societies; (2) to deny them the essential professional contacts with other physicians, and (3) to use the coercive power of the societies to deprive them of hospital facilities for their patients." [30] Upon the trial which followed, the American Medical Association and the Medical Society of the District of Columbia were convicted. They appealed but the convictions were affirmed, first, by the Circuit Court of Appeals for the District of Columbia and then by the Supreme Court.[31] The latter court avoided a decision on the "question whether a physician's practice of his profession constitutes trade under § 3 of the Sherman Act." But it held that: "Group Health is a membership corporation engaged in business or trade. Its corporate activity is the consummation of the cooperative effort of its members to obtain for themselves and their families medical service and hospitalization on a risk-sharing prepayment basis. The corporation collects its funds from members. With these funds physicians are employed and hospitalization procured on behalf of members and their dependents. The fact that it is coöperative, and procures service and facilities on behalf of its members only, does not remove its activities from the sphere of business.

"If, as we hold, the indictment charges a single conspiracy to restrain and obstruct this business it charges a conspiracy in restraint of trade or commerce within the statute. As the Court of Appeals properly remarked, the calling or occupation of the individual physicians charged as defendants is immaterial if the purpose and effect of their conspiracy was such obstruction and restraint of the business of Group Health."

At the same time that the American Medical Association was before the courts, a case was decided in Kentucky that may present another problem in restraint of trade. Dr. Hughes was a competent and qualified surgeon with a long and successful experience and with no proof against him of un-

professional conduct. In 1939 the superintendent of the Good Samaritan Hospital wrote to Dr. Hughes that in order for the hospital to continue as an accredited hospital, it would be necessary for him to have the indorsement of the proper board of officers of the American College of Surgeons. Apparently, Dr. Hughes was justified in interpreting this letter as denying him the use of the operating room in the hospital unless he ceased to perform some types of operations. For the letter was based on the fact that Dr. Hughes, "a general practitioner, had invaded the field of the specialist by performing certain operations, which are under rules usually performed in the hospital by surgeons classified as specialists, and such continued practice would take the hospital from the accredited list." Dr. Hughes sought an injunction to restrain the hospital from interfering with his practice. An injunction was refused, the court saying: "We have before us merely one question—his vested right to operate in the rooms of appellee hospital, when it for no manifested arbitrary or capricious reason, but in the exercise of a reasonable discretion to maintain its institution on an accredited basis, decided otherwise. Appellant has failed to demonstrate that he has such a vested right, either by contract, inherently or as vouchsafed by any constitutional provision, hence we are of the opinion that the chancellor properly dissolved restraining order and denied permanent injunction." [32]

There was no discussion of the possibility that the arrangement between the hospital and the American College of Surgeons was an agreement in restraint of trade and a possible violation of the Sherman Act, to say nothing of Kentucky statutes. Was the arrangement one that can be diffentiated from the conduct condemned in the Group Health case because it is a reasonable restraint since the primary, if not the sole, purpose was to maintain proper standards for hospitals? The present writer is not sufficiently versed in the complications of the Sherman Act to venture an answer to this question.

Compulsory Medical Attention

Professor Thomas Reed Powell has written about the constitutional aspects of compulsory vaccination and sterilization. But he confined his observations to cases decided by the United States Supreme Court.[33]

Not all of our state courts have been so favorably inclined toward the validity of compulsory medical treatment. The bulk of the litigation has concerned itself with vaccination against smallpox, as a condition of school attendance. As far as the writer is aware no state statute directly requiring such a vaccination has been held to be beyond the power of the state. But Illinois, not usually listed as politically and judicially progressive, has three cases in which a vaccination requirement was held to be invalid as beyond the delegated authority of the public body which attempted to enforce the requirement.[34] The mental obtuseness of these decisions is demonstrated to some extent by the opinion in a later Illinois case.[35] But even there the earlier decisions were distinguished because in the later case there was an

epidemic of smallpox, viz., about 40 cases in a city of approximately 12,000 population. Presumably there are those who can view with sweet tolerance the attitude of a supreme court that permitted the protection of vaccination only after the disease was a serious problem.[36] A Wisconsin decision fully supports the earlier Illinois decisions and more definitely condemned the vaccination regulation as unconstitutional.[37] Fortunately, however, it appears to be agreed that by one method or another most vaccination statutes and regulations have been held to be valid by the state courts, despite constitutional claims of equal protection, due process, non-delegation of legislative power, free public schools, religious and civil liberty, and freedom from unreasonable search and seizure.[38]

There was difficulty in Illinois in securing a statute that compelled under a penalty the dropping into the eyes of a baby within an hour after its birth 1 per cent solution of silver nitrate, or some equally effective prophylactic. Even though the purpose was to save eye-sight by preventing the disease of ophthalmia neonatorum, the Attorney-General of Illinois wrote an opinion declaring the proposed statute to be unconstitutional for interfering with the liberty of parents in rearing their children. The Governor accordingly vetoed the bill.[39] But this ridiculous position was too much for Illinois. The next legislature passed another bill and it was approved by Governor Horner. As far as is known no court test has been made of such legislation.

In November, 1919, George Buckner was in custody in the Topeka, Kansas, city jail. The city health officer, acting under a state statute, the rules of the state board of health, and a Topeka ordinance, examined Buckner and then certified that he was infected with chronic gonorrhea. Then followed an isolation order whereby Buckner would be sent to the Kansas State Quarantine Camp for men at Lansing for treatment. Buckner sought his release through a writ of habeas corpus. He failed and the Kansas Supreme Court held that the legislation was valid.[40]

New York in 1922 passed an act under which a "neglected" child was one whose parent refuses, when able to do so, to provide necessary medical, surgical, institutional, or hospital care for such child. The Children's Court had the power to order a child to be examined by a physician and whenever such a child appeared to be in need of medical or surgical care, to make an order for such treatment. Helen Vasko was brought before this court upon the petition of the Westchester County Society for the Prevention of Cruelty to Children. Medical examination disclosed that Helen, two years old, had a glioma of the retina of the left eye, which was permanently blind; that the growth was probably of a malignant nature and would increase until it filled the eyeball; that it would then burst through the eyeball and protrude between the lids; and that in all probability, if left to nature, it would follow the optic nerve into the brain, thus causing her death. An operation to remove the left eye was recommended with the advice that statistics show a cure in about 50 per cent of the cases. But Helen's parents refused to permit the operation, the mother saying that she would rather have the child

as she is now. "God gave her the baby and God can do what he wants." This attitude of the parents was thought by the New York court to be arbitrary. Accordingly, the statute was held to be constitutional and the order adjudging the child to be neglected was affirmed. As a necessary inference from the opinion the trial court's order included a direction that the operation be performed and this was also approved.[41]

Patricia Hudson presented a sad case. She had a congenital deformity consisting of an abnormal growth of her entire left arm which made that arm much longer and larger than the right arm and rendered it absolutely useless. The minority of the court from an examination of a photograph concluded that the left arm was ten times the size of the other arm and nearly as large as her body. The medical testimony was that Patricia appeared to be frail; that she will remain in a rather weakened condition, an easy prey for infection; that her heart is burdened by reason of having to pump blood through the large left arm; and that her chest and spine are becoming deformed from carrying the enormous weight. Both physicians concluded that there was no remedy except amputation which they recommended, even though "there is a fair degree of risk of life involved in the operation." Patricia came before a juvenile court on the complaint of an adult sister that Patricia was not receiving needed medical care. Patricia was then 11 years old. Her brothers and sisters testified that Patricia's deformed arm made her shy and sensitive and deprived her of a normal life. She did not attend school because other children jeered at her. Patricia apparently did not testify but she frequently cried and stated that she wished to have her left arm removed. Three of her sisters testified that they favored the amputation even though they realized that Patricia might not survive the operation. Her father was an invalid and a weak character. He testified that he would not object to the amputation and also stated: "I am leaving it in the Judge's hands." Her mother strongly opposed the operation, not because of religious scruples, even though she had had a divine healer for Patricia, but because of the danger of causing Patricia's death.

The trial judge ordered the amputation but the Washington Supreme Court by a vote of six to three reversed the order.[42] The majority opinion stated that the legal problem presented was whether Patricia's mother could be deprived of the control of Patricia for a sufficient period of time to subject Patricia to the operation which, in the judgment of the juvenile court, Patricia's welfare demanded.

The answer to this question was in the negative. Was it correct? One cannot give a negative answer to this last question without admitting that the Washington statute was in no sense as satisfactory and direct as the New York statute previously considered. Indeed it seems necessary to admit that the Washington juvenile court act was not drafted with any such problem specifically in mind. It has no express language providing for medical or surgical care. But it defined a dependent child as one who is destitute, or whose home, by reason of the neglect of a parent, is an unfit place for such

child, or one whose parent does not properly provide for such child, etc. The minority opinion argued that this language was sufficient and came to these conclusions: (1) "Medical services are necessary and a child who is not furnished such services is destitute;" and (2) since Patricia was in need of surgical attendance she was destitute and the juvenile court possessed the power to order the amputation.

In reaching these conclusions the minority relied on that part of the act which declared: "After acquiring jurisdiction over any child, the court shall have power to make . . . any order, which in the judgment of the court, would promote the child's health and welfare." The majority of the court appeared not to attach much value to this provision. Instead, it argued that under the same section, if the juvenile court found a child to be dependent, it was necessary to place the child under the legal control of somebody. "But the court may not, over objection of the natural guardian, or legal guardian or adoptive parents to whom custody and control of the child are awarded by the court, subject the child to a surgical operation."

Thus it is possible that the decision is primarily procedural in its significance. Instead of directly ordering the amputation, the juvenile court should have proceeded thus: (1) made a finding that Patricia was a neglected child under the statute; (2) made an order depriving her mother and father of her control and custody, taking care to have them transferred to a person, such as one of the adult sisters, who favored the amputation; (3) entertained a petition from this guardian asking for an amputation order, and; (4) made an amputation order in granting this petition. Whether this procedure would have been approved by the Supreme Court of Washington is doubtful. Despite the command of the legislature to give the juvenile court act a liberal construction, the majority of the court apparently failed to do so, or to heed the legal philosophy expressed by the New York court in the Rotkowitz case, even though it quoted this passage: "The law is a growth. It could not serve the purposes of man and his needs were it static, inflexible and rigid. Like life, the law constantly undergoes change—change which is imposed by life upon law." [43] In the course of an unnecessarily long opinion there is one paragraph in the Washington opinion that probably explains, beyond any merely logical setting forth of its reasons, the basic philosophy or perhaps the religious prejudice of the majority of the Washington court. It is worth quoting:

"As we read the evidence it is admitted by all concerned that there is a grave possibility that the child may not survive the ordeal of amputation; nevertheless, every one except the child's mother is willing, desirous, that the child be required to undergo the operation. Implicit in their position is their opinion that it would be preferable that the child die instead of going through life handicapped by the enlarged, deformed left arm. That may be to some today the humane, and in the future it may be the generally accepted, view. However, we have not advanced or retrograded to the stage where, in the name of mercy, we may lawfully decide that one shall be deprived of life

rather than continue to exist crippled or burdened with some abnormality. That right of decision is a prerogative of the Creator." This language, particularly the last sentence, reminds one of the excuse given by the mother of Helen Vasko in one of the New York cases. It was an excuse that the New York court thought was arbitrary. It is also odd that the majority of the Washington court criticized Patricia's mother, "who loves her child devotedly" for seeking "to shift responsibility of decision to the child at some future time, a present responsibility of the mother, a sacred duty the mother shirks." In any event it appears clear that despite a few vague references to constitutional rights, the Washington court did not decide Patricia's case on the theory that some principle of constitutional law would prevent the Washington legislature from amending its juvenile court act to conform to the New York acts. But it is regrettable that the majority of the Washington Supreme Court decided in favor of a static rather than a progressive view.

Enforcement of Standards

The normal method of compulsion if a person practises medicine or surgery without securing a license or after his license has been revoked or suspended is through a criminal proceeding with a jury trial. This method has not always been adequate. The statutory penalty may be so mild that it fails to deter some hardy individuals. More often, it seems, some quacks have a popular appeal and it is difficult if not impossible to convict them before a jury with sufficient frequency.

Iowa passed a statute that provided that a person who violated a law requiring a license for the practice of his profession could be restrained by a permanent injunction. This was in addition to a statute that made a medical practitioner subject to a fine and imprisonment for practising without a license. G. E. Fray became the defendant in an action to enjoin him from practising without a license. He complained that the first Iowa statute was unconstitutional because it deprived him of a jury trial as guaranteed by the Iowa constitution. But the Supreme Court ruled against him. The importance of this decision lies in the fact that an equity rather than a law court issues an injunction and that an equity court is not compelled to call a jury to determine the facts and very rarely does so. The assumption is that an equity judge has a higher I.Q. than the average jury, knows better from his experience how to evaluate evidence, and is less subject to prejudices and emotions. It is believed that quacks have less chance of avoiding the license law if the case is decided without a jury. In case the injunction issues, a claimed violation of the injunction decree will again be decided by the equity judge without the necessary use of a jury, unless a statute so requires. This method of enforcement of professional standards is also likely to be more speedy than a criminal proceeding. The Iowa Supreme Court admitted that this method could not be used in the ordinary prosecution of crimes. But for a long time equity courts have asserted jurisdiction over nuisances and

certain harms to property. Here the Iowa court made use of these analogies in favor of the public health and refused to hold the Iowa statute unconstitutional.[44] Other states have reached the same result and some of them have done so without the aid of a statute like the Iowa statute.[45] Still other states have refused to grant injunction decrees, holding that the criminal process would have to suffice.[46] In the last group of states three of the four cases concerned chiropractors. In the Illinois case it was asserted by the attorney general that some of the 52 individual defendants had been tried, convicted, and sentenced; that after paying their fines or serving their terms of imprisonment they returned and continued their practice, and that the Universal Chiropractors' Association collected dues from its members and paid all fines, costs, and attorneys' fees, thus creating disrespect for the law which makes it unlawful to treat human ailments without a license.

Limitations on Medical Practice

Dr. Samuel W. Lambert, "a distinguished physician" in 1922 in New York, sought to enjoin a federal prohibition director from interfering with his practice of prescribing vinous or spirituous liquors to his patients for medical purposes. The director was acting under congressional statutes which strictly limited the amount of liquor which physicians could prescribe. Dr. Lambert claimed that his constitutional right as a physician had been infringed even though, according to the majority of the court, he belonged to the minority group of physicians, who believed that liquor had value as a therapeutic agent. A bare majority of the Supreme Court of the United States decided that the statutes were not arbitrary. Accordingly Dr. Lambert was denied judicial relief.[47] The minority of the court challenged the assertion by the majority of the court that the views of the medical profession concerning vinous and spirituous, as distinguished from malt, liquors were opposed to their use as medicine. The minority of the court, accordingly, proceeded on the premise that vinous and spirituous liquors are of medical value.

Linder v. United States [48] should be contrasted with the Lambert case. Dr. Linder sold to a known female addict one morphine tablet and three cocaine tablets. His expectation was that the addict would administer them to herself in divided doses over a period of time. Nevertheless, he was convicted of violating the Harrison Narcotic Law. This conviction was affirmed by the Circuit Court of Appeals but was reversed and remanded by the Supreme Court. It is difficult to interpret the decision and opinion of the latter court. The opinion hardly seems justified in assuming "the doctor's good faith" and the wisdom of his action according to medical standards. It would appear that the decision resulted from the following factors: (1) it was a trivial case; (2) the Supreme Court has been closely divided as to the constitutionality of the Harrison Narcotic Law; and (3) it was announced that the law, a taxing act with penal provisions, must be

strictly construed. The court also announced that "direct control of medical practice in the states is beyond the power of the federal government." On the whole it is believed that the Linder case is of no particular importance as a precedent.

Contraceptives

There appears to be no doubt that the dispensing of contraceptives may be prohibited generally. To what extent, however, may physicians be compelled to accept such a prohibition? On the basis of the decided cases no final answer to this question will be ventured.[49] But it seems fair to observe that at least two recent decisions are unfavorable to the asserted constitutional right of physicians to prescribe the use of contraceptives even though they honestly believe that the use of contraceptives is desirable or necessary to protect the patient's health or life. Under this sort of a decision it would seem to follow that the patient has no constitutional right to have a physician advise him as to the necessity of using a contraceptive.

The first of these two decisions is Commonwealth v. Gardner which affirmed the conviction of a physician, a nurse, and two trained social workers. All worked for the North Shore Mothers' Health Office, a charitable organization. Two of them worked without pay and the contraceptive devices and medicine were sold and given in the office in accordance with the physician's instructions. No question was made concerning the physician's good faith. That seemed to be assumed. Despite that, the ruling of the trial court that these facts constituted no defense was approved. It was also held that the Massachusetts statute, prohibiting the dispensation of contraceptives, must be interpreted without qualification as applicable to physicians, and that, so interpreted, it was constitutional.[50] The Supreme Court of the United States blasted the appeal in this case by a dismissal "for the want of a substantial federal question." Nothing more was said and that would seem to be the equivalent of saying that the Supreme Court agreed with the Massachusetts court that the state statute as applied did not violate the national constitution, including the due process clause.[51]

Connecticut had a similar statute. Wilder Tileston, a licensed physician, sought a declaratory judgment to determine whether he was entitled to prescribe contraceptives for married women living with their husbands in the following cases: (1) patient is suffering from high blood pressure; if pregnancy occurred there would be imminent danger of toxemia of pregnancy which would have a 25 per cent chance of killing her; (2) patient is suffering from an arrested case of tuberculosis of the lungs of an acute and treacherous type so that if she should become pregnant such condition would be likely to light up the disease and set back her recovery for several years, and might result in her death; (3) patient is in good health except insofar as she has been weakened by having had three pregnancies in about 27 months and a new pregnancy would probably have a serious effect upon her general health and might result in permanent disability. Despite the ap-

pealing nature of these cases the Supreme Court of Connecticut decided that the statutes forbade Dr. Tileston from prescribing contraceptives for these patients even though that was his professional judgment. It also decided that the statutes, as interpreted, were constitutional.[52] Why? Because a physician in such cases need not prescribe contraceptives. All he needs to do is to advise his patients to refrain from sexual intercourse for the duration. Observe this language of the court: "The claim of the state on this point comes down, then, to a consideration of whether abstinence from intercourse is a reasonable and practicable method of preventing the unfortunate consequences. Certainly it is a sure remedy. Do the frailties of human nature and the uncertainties of human passions render it impracticable? That is a question for the legislature, and we cannot say it could not believe that the husband and wife would and should refrain when they both knew that intercourse would very likely result in a pregnancy which might bring about the death of the wife." Would and should! The will and the morality! This writer does not believe that either the will or obedience to the moral precept will exist in many instances. And he is inclined to believe that this significant restriction on freedom of belief and action, based upon a lack of realism as to sexual relations, would be better condemned as unconstitutional.

The Connecticut decision was appealed to the United States Supreme Court. Its decision was narrowly confined to a point of procedure. Curiously the attorneys for Dr. Tileston had raised in the Connecticut court only the question whether the statutes deprived "any person of life without due process of law." The Supreme Court of the United States held that "the proceedings in the state courts present no constitutional question which appellant has standing to assert. The sole constitutional attack upon the statutes under the Fourteenth Amendment is confined to their deprivation of life—obviously not appellant's [Tileston's] but his patients'. There is no allegation or proof that appellant's life is in danger. His patients are not parties to this proceeding and there is no basis on which we can say that he has standing to secure an adjudication of his patients' constitutional right to life, which they do not assert in their own behalf. * * * * No question is raised in the record with respect to the deprivation of appellants' liberty or property in contravention of the Fourteenth Amendment." [53]

NOTES

1. 272 U. S. 581, 47 S. Ct. 210 (1926).
2. For the benefit of the medical profession it is perhaps desirable to state that the term police power is just one way of expressing the idea that is better expressed by the words, regulatory power. Sometimes this regulatory power can be extended to a prohibition.
3. 129 U. S. 114, 9 S. Ct. 231 (1889).
4. Reetz v. Michigan, 188 U. S. 505, 23 S. Ct. 390 (1903); Watson v. Maryland, 218 U. S. 173, 30 S. Ct. 644 (1910—due process and equal protection); Collins v. Texas, 223 U. S. 288, 32 S. Ct. 286 (1912—osteopathy); Crane v. Johnson, 242 U. S. 339, 37 S. Ct.

176 (1917—drugless practitioner); Douglas v. Noble, 261 U. S. 165, 43 S. Ct. 303 (1923—dentists); Graves v. Minnesota, 272 U. S. 425, 47 S. Ct. 122 (1926—dentists; see citation of many state decisions); Sage-Allen Co. v. Wheeler, 119 Conn. 667, 179 Atl. 195, 98 A. L. R. 897 (1935—optometry). Cf. People v. Griffith, 280 Ill. 18, 117 N. E. 195 (1917—Act of 1915 to regulate optometry invalid).

5. Meffert v. Packer, 66 Kan. 710, 72 Pac. 247, 1 L. R. A. N. S. 811 (1903); Richardson v. Simpson, 88 Kan. 684, 129 Pac. 1128, 43 L. R. A. N. S. 911 (1913—dentist); Laughney v. Maybury, 145 Wash. 146, 259 Pac. 17, 54 A. L. R. 393 (1927—advertising); Yoshizawa v. Hewitt, 52 F. (2d) 411, 79 A. L. R. 317 (1931); State Dental Examiners v. Savelle, 90 Colo. 177, 8 Pac. (2d) 693, 82 A. L. R. 1176 (dentist practising as employee of a corporation).
6. Green v. Blanchard, 138 Ark. 137, 211 S. W. 375, 5 A. L. R. 84 (1919—dentist—divided court).
7. Laughney v. Maybury, 145 Wash. 146, 259 Pac. 17, 54 A. L. R. 393 (1927); McNaughton v. Johnson, 242 U. S. 344, 37 S. Ct. 178 (1917); People v. Witte, 315 Ill. 282, 146 N. E. 178, 37 A. L. R. 672 (1924).
8. Louisiana State Bd. of Medical Examiners v. Fife, 162 La. 681, 111 So. 58, 54 A. L. R. 594 (1926). While not precisely the same it appears impossible to reconcile satisfactorily with the Louisiana case, People v. Love, 298 Ill. 304, 131 N. E. 809, 16 A. L. R. 703 (1921) and People v. Schaeffer, 310 Ill. 574, 142 N. E. 248 (1924).
9. People v. Lewis, 233 Mich. 240, 206 N. W. 553 (1925—Michigan recognized chiropractors but held that one desiring to practice the system of chiropractic is not deprived of the equal protection of the laws by requiring him, as a condition for securing a license, to pass an examination in anatomy, histology, embryology, physiology, chemistry, bacteriology, pathology, diagnosis, hygiene, and public health, although such subjects are not taught in chiropractic schools).

   The board of regents of Texas University leased land to the city of Galveston for a municipal hospital, reserving the right to use part of the hospital for clinical instruction of university medical students. The hospital board in charge of the hospital excluded licensed osteopathic physicians from using this hospital. But this was held to be no violation of due process or equal protection. Hayman v. City of Galveston, 273 U. S. 414, 47 S. Ct. 363 (1927—"We cannot say that a regulation excluding from the conduct of a hospital the devotees of some of the numerous systems or methods of treating diseases authorized to practice in Texas, is unreasonable or arbitrary.")

   See for a more general discussion of equal protection, Iowa Ec. Med. College Ass'n. v. Schrader, 87 Ia. 659, 55 N. W. 24, 20 L. R. A. 355 (1893).
10. State ex rel. Walker v. Green, 112 Ind. 462, 14 N. E. 352 (1887); 136 A. L. R. 219 (Annotation). See, also, Fairfield v. Shellenberger, 135 Ia. 615, 113 N. W. 459 (1907—special license tax on traveling physicians). Cf. State v. Doran, 28 S. D. 486, 134 N. W. 53 (1912 occupation tax applicable only to non resident itinerant physicians invalid).
11. State v. Luscher, 157 Minn. 192, 195, N. W. 914 (1923).
12. York v. State, 144 Fla. 216, 197 So. 766 1 Loyola L. Rev. 109 (1940—It is not clear whether the peremptory writ of mandamus required the board to produce the examination papers of June 1939 in order to determine whether relator's grade entitled him to a certificate or whether it required the board to issue the certificate forthwith).
13. Semler v. Oregon State Board of Dental Examiners, 294 U. S. 608, 55 S. Ct. 570 (1935).
14. People by Kerner v. United Medical Service, 362 Ill. 442, 200 N. E. 157, 103 A. L. R. 1229 (1936). The opposite ruling was made in New York as to a chiropodist: People v. Dr. Scholl's Foot Comfort Shops, Inc., 277 N. Y. 151, 13 N. E. (2d) 750 (1938).
15. 12 Cal. (2d) 156, 82 P. (2d) 429, 119 A. L. R. 1284 (1938).
16. Butterworth v. Boyd, 12 Cal. (2d) 140, 82 P. (2d) 434, 126 A. L. R. 838 (1938).
17. California Physicians' Service v. Garrison, Cal. App. 155 P. 2d 885 (1945).
18. Group Health Ass'n v. Moor, 24 F. Supp. 445 (1938).

19. Jordan v. Group Health Ass'n., 107 F. 2d 239 (1939). See, however, U. S. v. American Medical Ass'n., 110 F. 2d 703 (1940) where the Circuit Court of Appeals was unable to say that the Group Health Association, Inc., as described in the indictment before the court, was illegally practising medicine.
20. See the opinion in U. S. v. American Medical Ass'n., 110 F. 2d 703, 714 (1940). Contrast 27 Marq. L. Rev. 135 (1943).
21. Jewell v. McCann, 95 Ohio St. 191, 116 N. E. 42 (1917)
22. Missouri ex rel. Hurwitz v. North, 271 U. S. 40, 46 S. Ct. 384 (1926).
23. Brinkley v. Hassig, 130 Kan. 874, 289 Pac. 64 (1930).
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25. Disqualification on the Ground of Bias as Applied to Administrative Tribunals, 23 The Canadian Bar Rev. 453 (1945); Re Segal and Smith, 5 Fed. C. C. Rep. 3 (1937).
26. State v. Schultz, 11 Mont. 429, 28 Pac. 643 (1892).
27. Dyment v. Board of Medical Examiners, 57 Calif. App. 260, 207 Pac. 409, 412 (1922); Bley v. Board of Dental Examiners, 120 Calif. App. 426, 7 P. 2d 1053 (1932); Kalman et al. v. Walsh et al., 355 Ill. 341, 189, N. E. 315 (1934); Abrams v. Jones, 35 Ida. 532, 207 Pac. 724 (1922).
28. U. S. v. American Medical Ass'n., 28 F. Supp. 752 (1939).
29. U. S. v. American Medical Ass'n., 110 F. 2d 703 (1940). See The Medical Profession and the Sherman Act, 8 Geo. Wash. L. Rev. 1034 (1940).
30. Ibid, at p. 711.
31. American Medical Ass'n. v. U. S., 130 F. 2d 233 (1942), 317 U. S. 519, 63 S. Ct. 326 (1943). See comments in 29 Corn. L. Qu. 271 (1943); 29 V. L. Rev. 832 (1943), 18 Tenn. L. Rev. 393 (1944).
32. Hughes v. Good Samaritan Hospital, 289 Ky. 123, 158 S. W. (2d) 159 (1942), reviewed in 31 Ky. L. Jr. 197 (1943).
33. Compulsory Vaccination and Sterilization: Constitutional Aspects, 21 N. C. L. Rev. 253 (1943).
34. Potts v. Breen, 167 Ill. 67, 47 N. E. 81 (1897—A rule of State Board of Health compelling vaccination of school children is unreasonable and beyond the power of the board where smallpox does not exist in the community and there was no reason for apprehension); Lawbaugh v. Board of Education, 177 Ill. 572, 52 N. E. 850 (1899); People v. Board of Education, 234 Ill. 422, 84 N. E. 1046 (1908).

    See also Burroughs v. Mortenson, 312 Ill. 163, 143 N. E. 457 (1924) and People v. Tait, 261 Ill. 197, 103 N. E. 750 (1913).
35. Hagler v. Larner, 284 Ill. 547, 120 N. E. 575 (1918).
36. The decision and the attitude of the Supreme Court of Illinois was much better in People ex rel. Barmore v. Robertson, 302 Ill. 422, 134 N. E. 815 (1922). There it was held that a typhoid carrier had been legally placed under a quarantine which required her to remain in her home and forbade her to prepare food for anyone except her husband and forbade anyone to come into her home, as a roomer or otherwise, unless he had been immunized from typhoid fever.
37. State ex rel. Adams v. Burdge, 95 Wis. 390, 70 N. W. 347 (1897). See a criticism of the Burdge case in Ex parte Company, 106 Oh. St. 50, 59, 139 N. E. 204 (1922).
38. Hartman v. May, 168 Miss. 477, 151 So. 737, 93 A. L. R. 1408 (1934). See also Zucht v. King, 260 U. S. 174, 43 S. Ct. 24 (1922).
39. See an editorial in 26 Ill. L. Rev. 785 (1932). People v. Pierson, 176 N. Y. 201, 68 N. E. 243 (1903) holds that a statute that makes it a misdemeanor wilfully to omit medical attendance for an adopted child did not violate the father's constitutional freedom of religion even though he believed in divine healing and not in physicians. See also Owens v. State, 6 Okla. Cr. Rep. 110, 116 Pac. 345 (1911).
40. Ex Parte McGee, 105 Kan. 574, 185 Pac. 14, 8 A. L. R. 831 (1919). See also People v. Thomas, 231 N. Y. S. 271, 133 Misc. Rep. 145 (1928—detention for blood test); In re Caselli, 62 Mont. 201, 204 Pac. 364 (1922); Ex parte Company, 106 Oh. St. 50,

139 N. E. 204 (1922); In re Travers 48 Cal. App. 764, 192 Pac. 454 (1920). Contrast Wragg v. Griffin, 185 Ia. 243, 170 N. W. 400 (1919) which appears to be a reactionary decision.

41. In re Vasko, 263 N. Y. S. 552, 238 App. Div. 128 (1933). This decision was the subject of comment in 12 Tenn. L. Rev. 59 (1933); 14 Boston U. L. Rev. 196 (1934); 28 Ill. L. Rev. 556 (1933).

In re Rotkowitz, 25 N. Y. S. 2d 624, 175 misc. 948 (1941) is a similar decision upon an order for an operation to correct and prevent extension of a leg deformity induced by poliomyelitis. The mother of the child petitioned for the order and the court found that the child was neglected by the father who would not consent to the operation. He gave no reason for his opposition.

42. In re Hudson, 13 Wn. (2d) 673, 126 P. 2d 765 (1942). The comment on this decision in 28 Ia. L. Rev. 372 (1943) is mildly critical: "Even in the absence of statute, the state's right of guardianship is superior to that of the parent if the assertion of the right is necessary for the welfare of the child. This authority should extend to an order for surgical care in a proper case."

43. 25 N. Y. S. 2d 624, 175 Misc. 948 (1941).

44. State v. Fray, 214 Iowa 53, 241 N. W. 663, 81 A. L. R. 286 (1932). See Legal Control of Medical Charlatanism, 22 N. C. L. Rev. 23 (1943) discussing and comparing the use of criminal prosecution, quo warranto, and injunction.

45. State ex rel. La Prade v. Smith, 43 Ariz. 131, 29 P. (2d) 718, 92 A. L. R. 168 (1934).

46. Dean v. State ex rel. Anderson, 151 Ga. 371, 106 S. E. 792 (1921); Redmond v. State ex rel. Attorney General, 152 Miss. 54, 118 So. 360 (1928—recommendation that state proceed by information to abate nuisance with a jury trial); State v. Maltby, 108 Neb. 578, 188 N. W. 175 (1922); People v. Chiropractors Ass'n., 302 Ill. 228, 134 N. E. 4 (1922).

47. Lambert v. Yellowley, 272 U. S. 581, 47 S. Ct. 210, 49 A. L. R. 575, 588 (1926).

Early Legislation Regulating The Practice of Medicine in 18 Ill. L. Rev. 225 (1923) is of general interest.

48. 268 U. S. 5, 45 S. Ct. 446 (1925).

49. See McConnell v. Knoxville, 172 Tenn. 190, 110 S. W. (2d) 478, 113 A. L. R. 966 (1937).

50. Commonwealth v. Gardner, 300 Mass. 372, N. E. 2d 222 (1938); 6 U. of Chic. L. Rev. 260 (1939) is critical of this decision. See also 50 Yale L. Jr. 682 (1941); 37 Mich. L. Rev. 317 (1938); 7 George Washington L. Rev. 255 (1938); 16 N. Y. U. L. Qu. Rev. 149 (1938).

51. Gardner v. Commonwealth of Massachusetts, 305 U. S. 559, 59 S. Ct. 90 (1938).

52. Tileston v. Ullman, 129 Conn. 84, 26 A. 2d 582 (1942). Two of the five judges dissented on the interpretation of the statute; but they said nothing about its constitutionality.

See 20 Boston U. L. Rev. 551 (1940); 3 Univ. of Det. L. Jr. 216 (1939).

53. Tileston v. Ullman, 318 U. S. 44, 63 S. Ct. 493 (1943).

CASE REPORTS

PULMONARY FILARIASIS *

By HAROLD RIFKIN,† Major, MC, AUS, and THEODORE P. EBERHARD, Major, MC, AUS

FILARIASIS, a disease formerly of interest to tropical medical practitioners, has become a problem which must now be recognized and managed by both medical officers and civilian physicians. Early in the war the disease was contracted by certain groups of American troops serving duty in filarial endemic areas in the South Pacific. Since the vector host is present in many areas in the Central Pacific, a continued incidence of the disease among our troops is a possibility. It seems important, therefore, to note all the clinical variants of the disease. The pathological findings, as manifested in natives, have been carefully worked out by Manson-Bahr [1] and O'Connor.[2] Essentially, there is lymph stasis and edema of the lymphatics associated with the presence of worms within the lumen. As the disease progresses, these foci undergo necrosis, with eosinophilic cellular infiltration of lymphatic wall. Eventually, there may be disintegration and calcification of the parasites, with peripheral infiltration of the lymphatic walls with macrophages, giant cells, lymphocytes, plasma cells, and fibroblasts. It is common opinion that the obstruction of lymph tracts produced by the tissue reaction surrounding the dying and dead worms accounts for the later picture of elephantiasis. The underlying morphological findings of early filariasis in American troops has been recently described by Michael,[3] Rifkin and Thompson,[4] Zuckerman and Hibbard,[5] and Wartman.[6] In all these series, there is distinct evidence of macrophagic proliferation, with fibroblastic overgrowth, and eventual fibrous obliteration of the involved lymphatics.

It is believed by many that a systemic reaction occurs either as a result of an allergic or a toxic reaction to breakdown of the worms. It has been possible to demonstrate that this acute hyperergic reaction may occur throughout the body, and is manifested by eosinophilia, edema, and hyperplasia of lymph nodes or edema and eosinophilic infiltration of the lymphatic walls. This may occur in areas far removed from the primary focus. It has been possible for us, in cases of suspected filariasis, to examine by biopsy the axillary and epitrochlear lymph nodes and lymphatics, when the primary focus appeared to be the right or left paminiform plexus. These para-focal nodes revealed lymph stasis, hyperplasia, and eosinophilia.

The sequelae of these progressive changes are usually increased intraluminal tension, with rupture of the lymphatics concerned, and spillage of lymph fluid into one of the organ or serous cavities. Craig and Faust [7] describe chyluria, secondary to ruptured lymphatics of the bladder or kidney. Strong [8] mentions chylocele developing as a result of increased tension, with rupture of the lymphatics of the tunica vaginalis. He further makes note of the fact that occa-

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sionally microfilariae are found in blood-stained sputum. He makes no mention of this phenomenon with associated pulmonary findings. In a recent editorial in the Naval Medical Bulletin,[9] a statement is made that "there is a pulmonic phase (in filariasis) manifested by a prevalent morning cough, (so) conspicuous in natives of endemic areas, which leads to a suspicion of widespread tuberculosis." This is noted as an example of the protean character of the disease. It has not been possible to find in the literature at hand recorded cases of proved pulmonary filariasis or filarial pneumonia.

We have recently had occasion to examine a South Pacific native who had been infected with filariasis (*W. bancrofti*) and whose clinical picture suggests the possibility of pulmonary filariasis.

Case Report

The patient was a 39-year old civilian laborer, who was a native from a South Pacific island where filariasis is endemic. With the exception of the latter three years

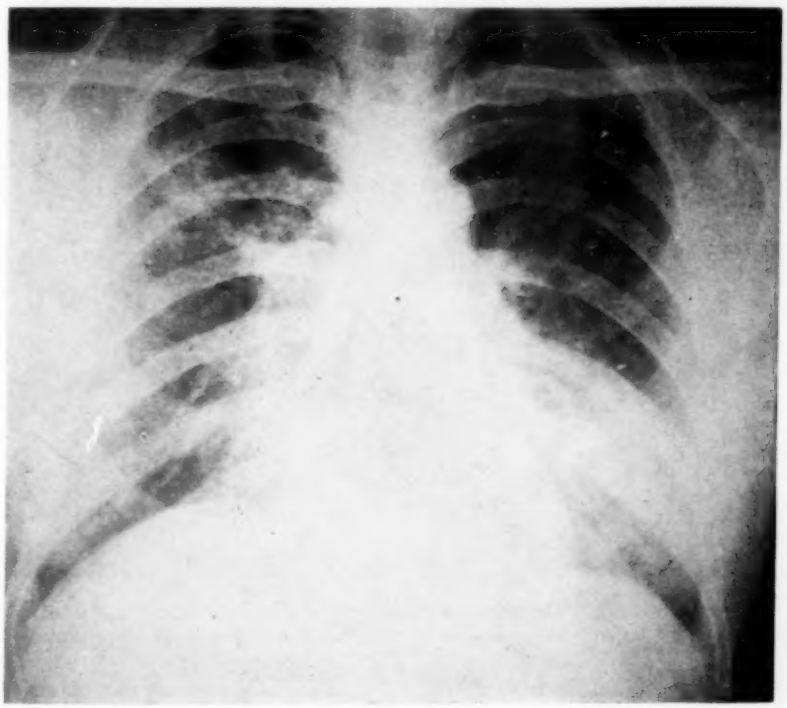

Fig. 1. December 2, 1943. Soft, diffuse shadow in left lower lobe and small ill-defined shadow in right upper lobe.

of his life, he had always lived on this island. He was admitted to a general hospital in the South Pacific region, having been transferred from a station hospital, because of hacking cough, expectoration of blood-stained sputum, and night sweats, of two years' duration. He complained of fatigue and malaise. No other symptoms referable to any other system were noted. Physical examination revealed an afebrile individual, of good build, who did not appear to be acutely ill. On admission, temperature was 98.8° F.; pulse 80 per minute; respirations 24 per minute; blood pressure

110 mm. Hg systolic and 70 mm. diastolic. Dullness, diminished breath sounds, and moist râles were noted in the right half of the chest, anteriorly and posteriorly and below the angle of the scapula on the left side, posteriorly. Lymphadenopathy was not present. There was no evidence of elephantiasis of the upper or lower extremities. The remainder of the physical examination was essentially negative. Admission diagnosis was tuberculosis, chronic, non-productive, moderately advanced.

Roentgenographic Examination: A film of the chest from another hospital taken December 2, 1943 (figure 1) showed a soft mottled diffuse shadow of increased density

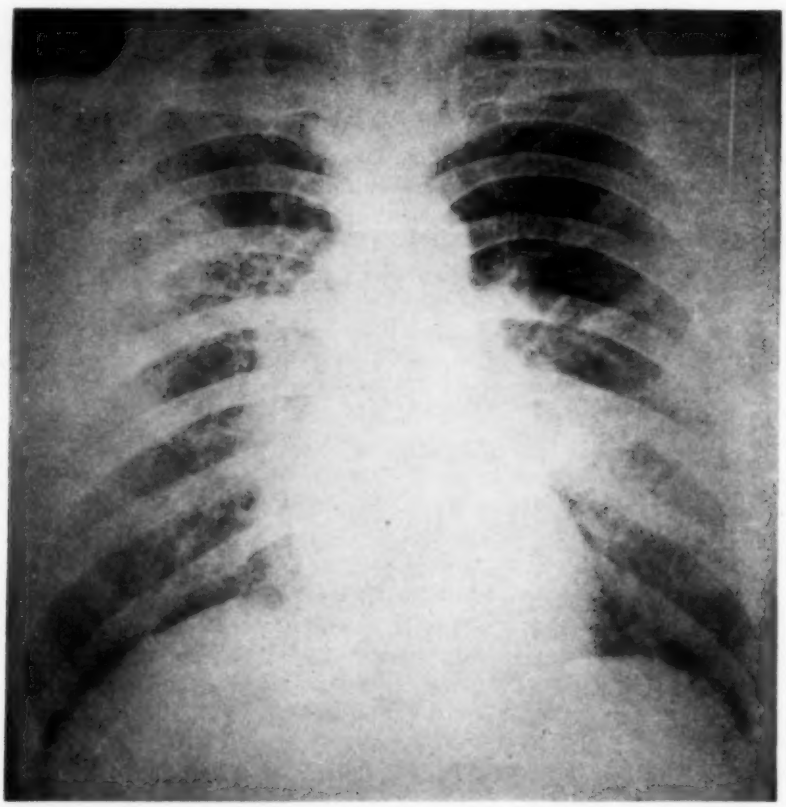

FIG. 2. January 16, 1944. The shadow in the right upper lobe has extended to almost the entire upper lobe and both shadows have become hard and linear.

fanning out from the left hilum into the lower lobe, and covering the lung field from the border of the eighth rib downward. The shadow became less dense below and laterally, leaving the lung margins almost clear. A shadow of the same character, but occupying an irregular localized area about 5 cm. in diameter, lay in the mid-zone of the right second anterior interspace. Heavy dense trunk markings connected this shadow with the hilum. The broncho-vascular markings were prominent throughout the lung fields.

A second transfer film, dated December 20, 1943, showed slight regression of the shadow in the left lower lobe, more contrast to the mottling, and beginning hard linear markings in the shadow on the right side. The small patch on the right had developed into a generalized fluffy density covering the entire lung field below the level of the anterior end of the third rib.

Our film (figure 2) taken on January 16, 1944, revealed marked regression of all of the shadows. The fluffy shadows of parenchymal infiltration had cleared, leaving in the left lower and right upper lobes rather fan-shaped zones of hard linear densities extending from the hila for varying distances into the lung fields.

Laboratory Data: The admission blood count revealed 4,450,000 red blood cells, 7,800 white blood cells, 92 per cent hemoglobin, 44 per cent neutrophiles, 25 per cent

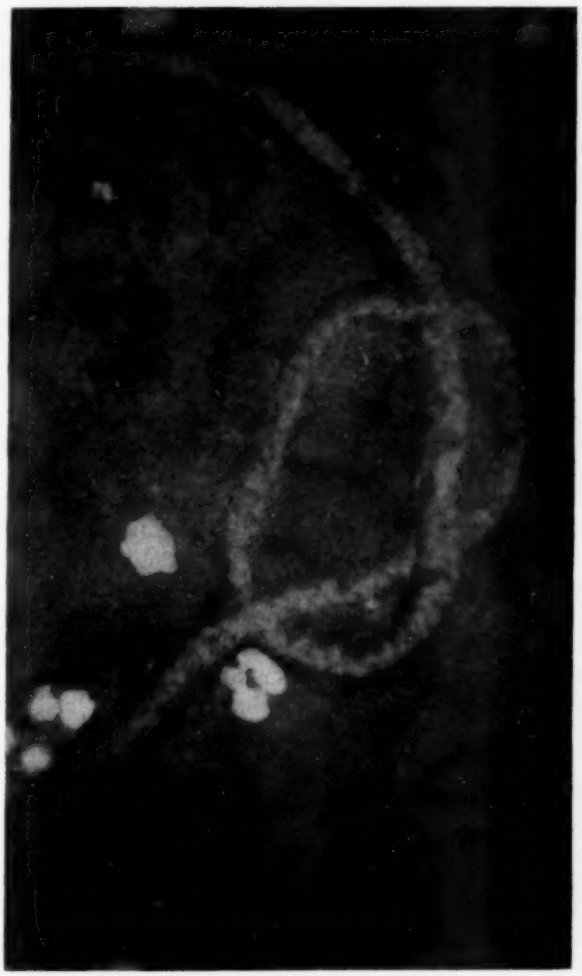

FIG. 3. Microfilaria in sputum smear (*W. bancrofti*). × 600.

lymphocytes, 28 per cent eosinophiles, 3 per cent monocytes; urine examination was negative; Kahn reaction was negative; malaria smears on four occasions revealed no plasmodium; sedimentation rate was 51 mm. (Wintrobe); examinations of four separate sputum concentrates revealed no acid fast bacilli; there was no evidence of yeasts, fungi, or molds. However, numerous microfilariae, characteristic of *Wuchereria bancrofti* were noted (figure 3). These were associated with many eosinophiles. Peripheral blood examination by the Knott concentration method [10] revealed a heavy

microfilarial infestation. A skin test,[11] utilizing *Dirofilaria immitis* antigen, gave a positive reaction to a titer of 1:8000 and 1:16000. Tuberculin test (PPD) was positive in a dilution of 1:10000. Because of the high eosinophile count, stool examinations were performed, and revealed many hookworm ova (type unidentified). "Cold agglutinin" studies were negative. A blood count repeated one week following admission revealed 8,400 white blood cells with 31 per cent eosinophiles. Otherwise no changes were noted. Sedimentation rate, one week after admission, revealed a drop to 40 mm. in one hour. Sputum cultures on two occasions revealed non-hemolytic streptococci.

Comment

The clinical findings, the serial roentgenograms, and the laboratory data offer a fertile field for differential diagnosis. The final roentgenogram, the absence of tubercle bacilli, and the clinical picture appear to rule out any active tuberculous infection. There was no proof of a mycotic lesion. The only organisms cultured from the sputum were non-hemolytic streptococci. This, together with the absence of a systemic reaction, the blood count, the rapidity of change in the roentgen-ray findings, and the chronicity of symptoms is against a bacterial infection. There is nothing to substantiate an amebic process. Pulmonary uncinariasis is to be considered, but the absence of hookworm parasites in the sputum and the duration of the symptoms appear to be unfavorable for such a diagnosis, although the possibility of an acute flareup during the larval migration through the bronchioles and alveoli must be considered. The examination of the serial films presents findings suggestive of an atypical pneumonia. The negative "cold agglutinin" reaction and the lack of clinical findings are against such a diagnosis.

The presence of microfilariae in the sputum can be explained on two bases: first, the patient had proved larval forms circulating in the blood stream, and it is possible that there may have been rupture of alveolar capillaries, with an outpouring of microfilariae into the alveoli; or second, the sub-mucosal lymphatics of the larger bronchioles and bronchi may have been involved in a generalized filarial infection, producing increased intraluminal tension, with resultant filarial bronchorrhea.

The findings of an eosinophilia and microfilariae in the sputum, associated with a positive skin test in a dilution of 1:16000, suggests the possibility of an acute filarial reaction involving the bronchial lymphatics. It is further suggested that the edema and eosinophilic infiltration of these lymphatics are responsible for the transitory pulmonary infiltrations noted on roentgenograms.

O'Connor [2] has previously expressed the view that filarial lymphangitis is allergic in character and results when there are sufficient amounts of protein liberated from the disintegration of dying or dead worms, to overcome "the resistance set up by previous sensitization." It is believed that when large amounts of protein are liberated, the typical inflammatory manifestations of filariasis result. With minimal amounts, the reaction may result in a localized urticaria or local pain or a transient rise in temperature. Although the primary focus, harboring the disintegrating adult worm, was not found here, there is no doubt in view of the microfilariae circulating in the peripheral blood, that such a focus existed.

SUMMARY

1. A case of a South Pacific island native is presented, whose clinical history, roentgenological, and laboratory findings suggest a diagnosis of pulmonary filariasis.

2. It is believed that these findings can be explained on the basis of an acute allergic reaction, part of the constitutional and systemic nature of the disease.

3. In view of the development of the disease in American troops, it is suggested that filariasis be considered in the future, in the differential diagnosis of transitory pulmonary infiltrations.

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TROPICAL EOSINOPHILIA *

By JOHN W. IRWIN, Capt., M.C., A.U.S., *Framingham, Massachusetts*

WEINGARTEN [1] has described a syndrome called tropical eosinophilia, which is characterized by frequent early morning paroxysms of asthma, weakness, loss of weight and appetite, and a marked leukocytosis which may reach 80,000, due chiefly to a marked increase in eosinophiles which may constitute as much as 80 per cent of the total number of white cells.

Weingarten,[1] who has had the opportunity to observe 81 cases, reported that all his cases except three originated in and about Bombay, India. He stated that the disease began with lassitude, a low-grade fever rising to 100° or 101° F., with a marked loss of appetite and a corresponding loss of weight. Within a

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week the patients developed a dry, ineffective cough which was more marked at night. Then the patients began to have severe attacks of wheezing, dyspnea, coughing, and tightness in the chest, which characteristically occurred in the early morning hours and responded to the adrenergic drugs. During the febrile period the spleen was moderately enlarged, hard, and smooth, but not tender. After a period of several weeks, the patients' temperatures became normal, and there was no further loss of weight. The laboratory examinations showed a marked leukocytosis ranging from 20,000 to 80,000, with eosinophiles as high as 88 per cent of the total white cell count. All the eosinophiles were of normal size and shape and fully matured. The sedimentation rate was moderately accelerated. Roentgenograms of the chest during the febrile period showed a distinctive, disseminated mottling of both lungs. The average focus was about the size of a split pea with moderate intensity of its central shadow and ill-defined blurred outlines. Each focus had a diameter of 0.2 to 0.5 cm. The foci were more numerous and larger about the hilar region and commoner in the bases than in the apices. This mottling usually lasted for about four weeks. Roentgenograms of the chest in cases which had become *chronic* showed only prominent bronchial markings.

The cause of this disease has not been established. However, Weingarten [1] has shown that the clinical symptoms disappear and that the laboratory findings revert to normal when the patients are treated with arsenicals. He treated his cases with intravenous neoarsphenamine, giving an injection every fourth day, usually in a course of six: 0.15 gm., 0.3 gm. and 0.45 gm., repeated once or twice. The neoarsphenamine was dissolved in a 10 per cent solution of calcium gluconate, to which 200 mg. of ascorbic acid were added. After the first two or three injections, he noted a slight increase in the total leukocyte count, as well as in the percentage of eosinophiles. After five or six injections, Weingarten observed a sharp decrease in the number of white cells and the percentage of eosinophiles. Clinical symptoms disappeared rapidly after the third injection.

Emerson [2] described a case of tropical eosinophilia in a young man of 30 years who worked in India from 1937 to the spring of 1942. His symptoms developed in December 1942 after his return to the United States and commission in the United States Naval Reserve. He showed the usual clinical symptoms, and his white cell count rose to 32,500, with 78 per cent eosinophiles. Roentgenograms of the chest showed fine, irregular, diffuse mottling. The areas of increased density were scattered throughout both lungs, but were more marked in the hilar regions and at the bases. Emerson [2] treated this case with two courses of carbarsone by mouth, using 0.25 gm. twice daily for 10 days with a 10 days' rest between the two courses. He noted a slight rise in the total white cell count half way through the first course of carbarsone. However, at the end of the first course of carbarsone there was a sudden drop in the total white cell count which was accompanied by a corresponding drop in the total number of eosinophiles. Following the second course of carbarsone, the total white cell count was normal with the eosinophiles making up 9 per cent of the total white count. Soon after the end of the first course of carbarsone the asthmatic paroxysms disappeared, the roentgenogram of the chest was clear, and auscultation of the chest revealed no abnormal findings.

Chaudhuri [3] saw a young male Mohammedan of 31 years of age in India with the clinical symptoms of tropical eosinophilia, a white cell count of 29,500, of

which 75.5 per cent were eosinophiles, and lungs showed by roentgenogram diffuse mottling. He was treated with intravenous mapharside injections, 0.02 gm. for the first and 0.04 gm. for four subsequent doses at five-day intervals. The clinical symptoms cleared, and the mottling of the lungs cleared after the third injection. Within four weeks the white cell count dropped to 6,200 with 16 per cent eosinophiles.

Parsons-Smith [4] treated a male European in Cairo, Egypt, who presented the clinical symptoms and laboratory picture of tropical eosinophilia, with neoarsphenamine as did Weingarten, and he obtained the usual restoration to health of his patient.

Robert Helig and S. K. Visveswar [5] treated two cases of tropical eosinophilia in India successfully with neoarsphenamine. They felt that the disease might have an allergic origin.

S. K. Vaidya [6] diagnosed six cases of tropical eosinophilia from 1929 to 1934. He recommended that these patients be treated with neoarsphenamine intravenously. Fellow medical men treated these cases and clinical cures were obtained. It is interesting to observe that two of these cases had frequent relapses and had to be treated with arsenicals during each relapse. Vaidya stated that tropical eosinophilia may only be cases of asthma and allied allergic conditions giving an extreme allergic response.

Menon [7] analyzed eight cases of tropical eosinophilia which he saw in India. He found that it was most common below the age of 30 years, and more common in males than in females. He found that the white blood cell count varied between 15,000 and 25,000. The eosinophilia was between 32 per cent and 67.5 per cent, and the sedimentation rate was increased. He suggested that this syndrome of tropical eosinophilia was due to an infection, the responsible organism being yet unidentified.

Lal [8] saw 15 cases of tropical eosinophilia in India. He found that arsenical medication resulted in clinical cures.

Hirst and McCann [9] reported a case of tropical eosinophilia in a United States Naval officer who developed symptoms while stationed in Samoa. When they saw the officer, he had had symptoms for two years. They obtained a clinical cure with intravenous neoarsphenamine as outlined by Weingarten. They failed to find the cause of this syndrome.

van der Sar and Hartz [10] saw three cases of tropical eosinophilia on Curaçao. In one case they demonstrated microfilariae in the eosinophilic abscesses and in the enlarged axillary lymph nodes. They were unable to demonstrate microfilariae in the enlarged lymph nodes of their other two cases. They viewed an autopsy in a fourth case, in which blood in the liver showed hypereosinophilia. The spleen was enlarged and the subcapsular pulp showed many eosinophiles and microfilariae. They treated their three cases successfully with arsenicals. They felt that they had demonstrated the relationship between tropical eosinophilia and filariasis. They also felt that the discussion of the treatment of filariasis with arsenic should be studied further.

In April 1944 two patients were admitted to the Cushing General Hospital with a diagnosis of bronchial asthma. Early in the morning on the day of their admission, both patients developed what appeared to be a typical paroxysm of asthma which was relieved in each case by 0.5 c.c. of epinephrine (1–1000) subcutaneously. However, they both showed elevated white blood cell counts,

15,000 in one case and 25,000 in the second patient, with a marked eosinophilia, 45 per cent in one patient and 60 per cent in the second case. I thought of Dr. Francis M. Rackemann's [11] statement: "All is not allergy that wheezes." In discussing the patients with Colonel John A. Isherwood, I found that a marked eosinophilia with respiratory symptoms has been seen in tropical areas. He suggested the diagnosis of tropical eosinophilia, and referred me to Emerson's [2] paper.

Case Reports

Case 1. A 34-year-old white soldier entered the Army March 13, 1941. His past medical history revealed that the patient had had the usual symptoms of hay fever with some wheezing and dyspnea from mid-August until the first frost each year from 1923 to 1936. From 1936 he had only mild lacrimation and sneezing during his usual hay-fever season. There were no other allergic manifestations in himself or in his family. Without difficulty he completed 11 months' training as an infantry rifleman in Florida, Georgia, and Louisiana. After 21 months of service in the Southwest Pacific theater, in October 1943 he developed a severe, chronic, nonproductive cough. About two weeks later during the early hours of the morning he had severe paroxysms of wheezing, dyspnea, coughing, and tightness of his chest, which persisted for several hours. Every morning for a month his attacks continued. He lost weight and became listless. Then he was admitted to an army hospital.

There, on physical examination his chest was found to be full of sibilant and sonorous râles with occasional crackling and crepitant râles, both inspiratory and expiratory. His vital capacity averaged 2700 c.c. with no change with the use of epinephrine. During his 45 days at this hospital, his total white cell count averaged 30,000 with 75 per cent eosinophiles; repeated stool examinations were negative for ova and parasites; urine and sputum showed no ova or cysts; roentgenograms of skull and soft tissues were negative; and microscopic study of the sternal bone marrow revealed only marked hyperplasia of the eosinophilic elements of the marrow. During his stay at this hospital his weight declined from 136 to 124 pounds, and the paroxysms of coughing, wheezing, and dyspnea became more severe and appeared throughout the 24 hours, in contrast to his previous episodes, which had appeared only in the early hours of the morning.

On December 19, 1943 the patient was transferred to a Naval Hospital. He remained there for one-and-a-half months, and his clinical symptoms and laboratory picture showed no change. Then the patient was sent to a numbered General Hospital, where chest examination revealed poor expansion on inspiration, increased resonance, diminished breath sounds, moist and musical râles with wheezing throughout both lungs. A chest plate showed a slight diffuse pleural thickening and possible slight pulmonary fibrosis. The patient was evacuated from the Southwest Pacific theater on February 8, 1944, and he arrived at the Dibble General Hospital on February 22, 1944. For two months the patient's condition remained unchanged.

The patient arrived at the Cushing General Hospital on April 13, 1944. On admission he weighed 126½ pounds; blood pressure was 128 mm. Hg systolic and 80 mm. diastolic; pulse rate was 90 per minute; respirations were 22 per minute; and temperature was 98.6° F. He was found to have an asymptomatic pilonidal cyst and a deviated nasal septum. Cervical, inguinal, and submaxillary lymph nodes were palpated. The costo-phrenic angle was moderately widened, and there was some flaring of the ribs. The anterior-posterior diameter of the chest was moderately increased. Chest was hyperresonant throughout to percussion. On auscultation of lungs, breath sounds were distant and expiratory wheezes were noted in all lung fields. His vital capacity was 60 per cent of normal. In the early hours of his first morning at Cushing, the patient was awakened with a severe paroxysm of wheezing, coughing, dyspnea.

and tightness in the chest. The respiratory rate rose to 60 per minute. All lung fields were filled with both inspiratory and expiratory musical râles. The attack was relieved with 0.5 c.c. of epinephrine (1–1000) subcutaneously. He continued to have similar paroxysms of wheezing, etc., every morning, usually between the hours of one and five. The use of a saturated potassium iodide mixture and ephedrine capsules definitely lessened the severity of these episodes.

Prior to arsenical treatment, his total white cell count varied from 30,000 to 70,000, with an eosinophilia of 60 to 90 per cent. Sedimentation rate was 24 mm. per hour on admission, platelets numbered 209,000. Repeated examination of the blood for malarial parasites and microfilariae failed to show any organisms. Repeated blood cultures were negative. Kahn, agglutination test for undulant fever, Weil-Felix test, and heterophile antibody test were normal.

A few eosinophiles, no Curschmann spirals, no tubercle bacilli, and a few epithelial cells were found in the sputum. Sputum cultures were negative for molds and fungi. An occasional erythrocyte and a few leukocytes were seen in the urine, and a catheterized specimen of urine on culture was negative. Feces repeatedly were free of parasites and ova. Repeated cultures of feces yielded only *Bacillus aerogenes.*

Microscopic examination of sternal bone marrow presented an increase in eosinophiles which were mature and normal in size and shape. Dark field and microscopic examination of a cervical lymph node and a piece of adjoining muscle was negative for organisms. The cervical lymph node contained a few normal eosinophiles. The structure of the cervical muscle was normal. Cultures of the cervical lymph node and muscle were negative.

Intradermal skin tests for Echinococci and Trichinellae were negative. The pure protein skin test for tuberculosis was positive (4 +) for the second strength.

Intracutaneous skin tests for dust, the animal epitheliums, orris root, and several of the pollens, including ragweed, timothy, and orchard grass, were positive.

Roentgenograms of the nasal sinuses showed haziness of both antra, with a marked thickening of the lining membrane on both sides. An increase of the bronchial markings of each hilar zone and in the upper portion of the right lung and a thickening of the interlobar pleura on the right was seen in stereoscopic films of the chest.

On May 23, 1944 the patient was placed on 0.25 gm. of carbarsone orally twice daily. He completed two 10-day courses of carbarsone, with a 10-day rest period between courses, on June 21, 1944. His acute paroxysms of coughing, wheezing, dyspnea, and tightness in the chest continued until July 3, 1944, at which time the attacks ceased. However, patient continued to have a few expiratory musical râles scattered throughout all lung fields. By July 27, 1944 patient was symptom-free except for some mild wheezing each morning at about five. Steadily he gained weight and energy. Then he was given the following course of neoarsphenamine intravenously: July 27, 1944, 0.15 gm.; July 31, 1944, 0.3 gm.; August 4, 1944, 0.45 gm.; and August 8, 1944, 0.45 gm. Following this course of neoarsphenamine, patient was symptom-free, and his chest was clear. He continued to gain weight and strength, weighing 145 pounds on September 11, 1944. By August 8, 1944 a roentgenogram of the chest showed only slight thickening of the interlobar pleura on the right. The intradermal skin tests for dust, feathers, ragweed, and timothy were more markedly positive in September 1944 than in April 1944. However, this could be accounted for by the fact that the patient was having some mild hay fever in September due to ragweed pollen.

Figure 1 graphically pictures his white cell count, eosinophilia, and sedimentation rate throughout the course of his illness. It is to be noted that arsenic increased the white cell count and percentage of eosinophiles at first. However, both dropped dramatically after a few days' treatment.

OCT 1943
NOV 1943
DEC 1943
FEB 1944
APRIL 1944
MAY 1944
JUNE 1944
JULY 1944
AUG 1944
SEPT 1944
WHITE BLOOD COUNT
EOSINOPHILES
SEDIMENTATION RATE
MAY FIRST COURSE CARBARSONE STARTED
1 JUNE FIRST COURSE CARBARSONE STOPPED
11 JUNE SECOND COURSE CARBARSONE STARTED
21 JUNE SECOND COURSE CARBARSONE STOPPED
11 JULY NEOARSPHENAMINE .15 GRAM IV
21 JULY NEOARSPHENAMINE .30 GRAM IV
4 AUG NEOARSPHENAMINE .45 GRAM IV
8 AUG NEOARSPHENAMINE .45 GRAM IV

Fig. 1. Case 1.

In June 1945 the patient was seen at the Lovell General Hospital. The patient was feeling well and was working in a woolen mill. On a few occasions he had noticed some mild wheezing on getting up in the morning. However, he had not had any dyspnea. He showed nothing abnormal on physical examination. He weighed 158 pounds. His total white cell count was 8,000 with 11 per cent eosinophiles, 51 per cent neutrophiles, 35 per cent lymphocytes, and 2 per cent monocytes.

Dr. Harold W. Brown of the School of Public Health, Columbia University, supplied me with *Dirofilaria immitis* antigen for intradermal skin testing. The preparations used were prepared by Eli Lilly and Company, and include 1–1000 dilution B 7615 A, 1–10,000 dilution B 7615 A, and a control B 7615 D. The quantity of each solution injected intradermally was 0.01 c.c. A reaction was considered positive when the wheal of the antigen exceeded 3 mm. or more that of the control wheal. The patient showed positive reaction to both dilutions at 15 minutes, at 30 minutes, at 40 minutes, and at one hour.

Case 2. A 26 year old white soldier entered the Army in October 1939. His medical history was negative for allergic diseases and their manifestations. With the exception of one sister who had mild "rose fever" in June and July of each year, the entire family was free of allergy. This "rose fever" had never been investigated medically.

Without difficulty the patient completed 26 months of infantry training in the southern section of the United States. In January 1942 he went to the islands in the Southwest Pacific theater. After 18 months in that area, in July 1943 one morning at about 4:30 a.m., patient was awakened by a severe, dry, nonproductive cough. Within the same week he began to have severe attacks of wheezing, dyspnea, coughing, and tightness in the upper anterior-posterior portion of his chest. The attacks were frequent, occurring every two to four hours and lasting 15 to 30 minutes. Gradually he lost his appetite, lost weight, and became weak. On October 30, 1943 he was admitted to an Army hospital, where he was found to have an eosinophilia of 72 per cent. He remained at this installation for two months, during which time his symptoms became more marked, particularly in the early morning hours. His weight continued to drop, and he became weaker. Repeated stool examinations showed no ova or parasites. Microscopic examination of an inguinal lymph node and sternal bone marrow showed only a marked increase in normal eosinophiles.

In December 1943, patient was transferred to a Naval Hospital. On physical examination he appeared undernourished; temperature 99.2° F.; pulse 84 per minute; and respirations 16 per minute. Throughout both lungs, most prominent at the bases and more prominent after coughing, were many sibilant and sonorous râles. Attacks of wheezing, dyspnea, and coughing appeared more frequently and severely at night. These attacks were relieved by epinephrine subcutaneously. Laboratory examinations showed: average total white cell count was 15,000, with 44 per cent eosinophiles; roentgenograms of chest showed a slight generalized fibrosis of both sides of the chest; sputum contained no acid-fast organisms, a few streptococci, and a few staphylococci; repeated stool examinations were negative for ova and parasites. He was evacuated from the Southwest Pacific theater on February 8, 1944, and arrived at the Dibble General Hospital February 22, 1944, where his symptoms and laboratory picture remained unchanged for two months.

On arrival at the Cushing General Hospital April 13, 1944, the patient weighed 108 pounds; blood pressure was 122 mm. Hg systolic and 72 mm. diastolic; radial pulse, 76 per minute; respirations, 20 per minute; temperature, 98.4° F.; and vital capacity 85 per cent of normal. Inguinal and axillary lymph nodes the size of almonds were palpated. The costophrenic angle was slightly widened, and the anteroposterior diameter of the chest was slightly increased. Chest was resonant to percussion. A few moist inspiratory râles were noted at the bases of both lungs, and a few expiratory

wheezes were found scattered throughout all lung fields. The expiratory phase of respiration was slightly increased.

In the early hours of his first morning at Cushing, the patient was awakened by a severe paroxysm of wheezing, dyspnea, coughing, and tightness in his chest. His respiratory rate rose to 35 per minute. All lung fields were filled with both inspiratory and expiratory musical râles. The attack was relieved by 0.25 c.c. of epinephrine (1–1000) subcutaneously. The patient continued to have similar paroxysms every morning between the hours of one and five. The use of a potassium iodide mixture and ephedrine capsules definitely lessened the severity of these attacks.

His total white cell count fluctuated between 20,000 and 25,000, with 50 per cent to 70 per cent eosinophiles. Sedimentation rate averaged 7 mm. per hour. Platelets numbered 221,900. Repeated examinations of the blood failed to show any malarial parasites or microfilariae. Repeated blood cultures were negative for any organisms. Kahn, agglutination test for undulant fever, Weil-Felix test, and heterophile antibody test showed no abnormalities.

Sputum examinations revealed a few eosinophiles, with no fungi, no molds, no acid-fast organisms, and no Curschmann spirals. Cultures of the sputum for molds and fungi were negative. Catheterized specimen of urine produced a few colonies of *Staphylococcus albus* on culture. Repeated stool examinations for ova and parasites were negative.

Sternal bone marrow contained an increased number of normal mature eosinophiles. Dark-field examination of an axillary lymph node and adjoining piece of muscle showed no organisms. Microscopic section of the lymph node and muscle was normal, and cultures of both revealed no organisms.

Intradermal skin tests for Echinococcus and Trichinella were negative. The pure protein derivative skin test for tuberculosis gave a positive (2+) reaction for the second strength. Patient showed positive intradermal skin tests to dust, mixed feathers, kapok, wool, orris root, and tobacco.

Roentgenograms of the paranasal sinuses were clear, and those of the chest showed an increase in density of the bronchial markings on both sides and a thickening of the interlobar pleura on the right.

On May 23, 1944, the patient started a 10-day course of 0.25 gm. of carbarsone orally twice daily. He had two courses with a 10-day rest between them, finishing the second course on June 21, 1944. Immediately following the initiation of arsenical therapy, his asthmatic-like paroxysms increased in frequency and severity. He had to be placed in an oxygen tent. He became epinephrine fast, and he was treated successfully with ether in olive oil by rectum. On May 27, 1944, his asthmatic-like paroxysms suddenly ceased. However, he continued to have expiratory musical râles throughout all lung fields and mild coughing until June 2, 1944, one day after the last day of the first course of carbarsone, at which time his coughing ceased and only a few scattered expiratory musical râles remained. He began to gain weight and regain his energy. By June 7, 1944 all lung fields were completely clear, and he had no further symptoms. On August 16, 1944, his vital capacity was 112 per cent of normal, and he weighed 118 pounds. His platelet count rose to 300,000. On August 19, 1944, intradermal skin tests showed positive reactions to dust, cow epithelium, dog epithelium, goat epithelium, rabbit epithelium, feathers, kapok, wool, orris root, and tobacco. Following arsenical therapy, his urine was normal. On September 14, 1944 a roentgenogram of his chest was normal.

Figure 2 graphically pictures his total white blood cell count, percentage of eosinophiles, and sedimentation rate in mm. per hour throughout the course of his illness. It shows that arsenical therapy increased his white cell count and percentage of eosinophiles at first. However, with a few days of therapy the white cell count and percentage of eosinophiles began to show a dramatic decrease.


OCT 1943
NOV 1943
DEC 1943
FEB 1944
APRIL 1944
MAY 1944
JUNE 1944
JULY 1944
AUG 1944
SEPT 1944
WHITE BLOOD COUNT
EOSINOPHILES
SEDIMENTATION RATE
23 MAY FIRST COURSE CARBARSONE STARTED
1 JUNE FIRST COURSE CARBARSONE STOPPED
11 JUNE SECOND COURSE CARBARSONE STARTED
23 JUNE SECOND COURSE CARBARSONE STOPPED

FIG. 2. Case 2.

On February 24, 1945 the patient was seen at his home. He had been feeling well, and was holding a position that required moderate physical exertion. On a few occasions on getting up in the morning he had noted some mild wheezing, which would persist for only a few moments. At no time had he experienced dyspnea, coughing, tightness in his chest. On physical examination nothing abnormal was noted. He weighed 110 pounds. His total white cell count was 13,200 with 61 per cent polymorphonuclear leukocytes, 8 per cent eosinophiles, 27 per cent lymphocytes, and 4 per cent monocytes.

In June 1945 he was seen at the Lovell General Hospital. He continued to feel well, and he weighed 115 pounds. Nothing abnormal was noted on physical examination. Intradermal skin tests were made with 1–1000 dilution and 1–10,000 dilution of *Dirofilaria immitis* and the control as prepared by Eli Lilly and Company. His tests were positive to both dilutions at the end of 15 minutes, 30 minutes, 45 minutes, and one hour. A reaction was considered positive when the diameter of the antigen wheal exceeded by 3 mm. or more that of the control wheal. His white blood cell count was 7,750, with 4 per cent eosinophiles, 61 per cent polymorphonuclear leukocytes, 33 per cent lymphocytes, and 2 per cent monocytes.

Differential Diagnosis: Colonel Johnson McGuire followed these cases with interest, and gave many helpful suggestions in establishing the diagnosis.

Since these patients spent considerable time in areas known to be heavily infested with many pathogenic parasites, various parasitic infections were considered. No parasites or ova were recovered in the blood, in the feces, in the urine, or in the sputum of either patient either at Cushing or overseas installations, although frequent and varied procedures were tried. No ova of *Schistosoma mansoni* or of *Ascaris lumbricoides,* no cysts, nor trophozoites of *Entameba histolytica* were recovered.

Ankylostomiasis was ruled out. Neither of the patients had an anemia, although they had suffered from their disease for many months. The patients did not experience palpitation, epigastric tenderness, or a tendency to mental retardation. Neither patient had chronic constipation or diarrhea. Repeated stool examinations in several medical installations revealed no hookworm ova.

All agglutination tests were negative, including Weil-Felix, heterophile antibody, and the agglutination test for undulant fever. Intradermal skin tests for Ecchinococci and Trichinellae were negative. Muscle biopsy failed to support a diagnosis of trichinosis. Attempts to culture any yeast or fungus from the sputum failed.

Loeffler's syndrome was considered. This disease is usually accompanied by a rise in temperature, cough, wheezing, and a metallic taste. Physical examination usually reveals some sibilant râles throughout the lung fields, with areas of diminished resonance. Jones and Souders [12] reported cases with a total white cell count of 10,000, with 10 per cent to 60 per cent eosinophilia. Roentgenograms show abnormal shadows that appear and disappear rapidly, only to reappear in another lung field. These roentgenographic findings are not consistent with those in the cases presented. Moreover, Loeffler's syndrome does not run as long a course as that of the cases described.

Hodgkin's disease and eosinophilic leukemia were considered. Since both patients are now quite well, it would seem fair to consider that they did not have either of these diseases.

Periarteritis nodosa could present a similar clinical and laboratory picture. However, both patients showed no tender muscles or painful nodes and had

normal blood pressure. In both cases there was an absence of peripheral neuritis. Muscle biopsy in both cases showed normal vascular tissue.

Bronchial asthma does not present a comparable laboratory picture.

Dr. Francis M. Rackemann examined both patients. He was of the opinion that neither patient had ordinary bronchial asthma or the type classified as periarteritis.

Filariasis was considered, as both patients had spent considerable time in an area where *Wuchereria bancrofti* abounds. Repeated examinations of the blood of both patients at all hours revealed no microfilariae. Examination of biopsies of enlarged lymph nodes, muscle tissue, and bone marrow failed to show any filariae. However, both patients have positive reactions to intradermal skin testing with *Dirofilaria immitis* antigen. Bozicevich and Hutter [13] found that a 1:1,000 dilution of *Dirofilaria immitis* antigen gave false positive reactions in approximately 30 per cent of people not exposed to filariasis. They found that the number of false positives could be markedly reduced by using a 1:8,000 dilution of *Dirofilaria immitis* antigen. The patients presented had no enlargement of lymph nodes after their treatment with arsenicals.

Summary

Two cases similar to those described by Weingarten [1] as tropical eosinophilia have been presented.

These cases originated in the Southwest Pacific area.

Careful clinical and laboratory study failed to establish the etiology of the disease. I feel that the possibility of tropical eosinophilia being filariasis must be kept in mind as van der Sar and Hartz [10] have seen cases of tropical eosinophilia in whom they have found microfilariae. All future cases should be thoroughly searched for microfilariae.

Both cases responded to arsenical therapy. It would seem that intravenous arsenical treatment is more effective than oral therapy.

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PENICILLIN IN THE TREATMENT OF HISTOPLASMOSIS: TWO CASE REPORTS *

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IN the past five years, histoplasmosis has been encountered with increasing frequency at the University of Michigan Hospital. In part, this may be due to a greater awareness of the disease, but this does not seem entirely to account for its increased incidence. Since December 1944, four cases of histoplasmosis have been diagnosed ante mortem at the University Hospital and variously treated. The present report is concerned with the treatment with penicillin of one of these cases, together with another case admitted to the hospital prior to 1945. None of these cases is included in the review by Parsons and Zarafonetis.[1]

CASE REPORTS

R. Y., a 55 year old white male, was admitted to the hospital on June 2, 1943 complaining of perineal pain, pain on defecation, and recent chills and fever. In July 1942 he noted the onset of severe sharp shooting pains in the left inguinal region, radiating to the suprapubic region and penis. This pain persisted and was unchanged at the time of admission.

Rectal examination had revealed what was interpreted as carcinoma of the prostate, and for this he had been given 2 mg. of stilbesterol daily for four months followed by roentgen-ray castration.

In September 1942 a roentgen-ray diagnosis of gastric ulcer was made, and in January 1943 a partial gastric resection was done. The pathological diagnosis was subacute purulent gastritis. Foreign-body giant cells and large collections of eosinophiles were present.

Two weeks prior to admission to the University Hospital the patient developed diarrhea, chills, fever, and severe dysuria.

After admission two cystoscopic examinations revealed chronic active trigonitis with lesions of cystitis cystica in various stages of development. This was believed to be secondary to an extra-vesical inflammatory process. Biopsies revealed polypoid fragments of bladder mucosa showing active chronic inflammation. Sigmoidoscopy demonstrated an extra-rectal mass which was extremely tender and about 6 cm. above the anus. Biopsy revealed atrophic catarrhal proctitis. Beneath the mucosa there was a single granulomatous focus with necrotic material in the center. Colon roentgenograms were interpreted as showing a narrowing and irregularity probably due to an extrarectal mass. Para-rectal surgical exploration yielded no evidence of an inflammatory or neoplastic mass of any kind. Chest roentgenogram on June 4, 1943 was negative. The hemoglobin was 13.1 gm. and the sedimentation rate was elevated. The white blood cell count was normal. Urinalysis showed a few white blood cells and mixed organisms. Blood serologic reaction was negative. He was discharged on June 6, 1943 with the diagnoses of chronic trigonitis with cystitis cystica and questionable old seminal vesiculitis.

He was readmitted to the hospital on Dec. 8, 1944 because of weakness and fever. He stated that subsequent to his discharge in June 1943, his weakness, ease of fatigue, and rectal pain gradually subsided over a six month period. He had no further rectal or inguinal pain and had returned to strenuous work. In August 1944 he developed

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From the University Hospital, Ann Arbor, Michigan.

severe bilateral temporal headache, chills, fever, and night sweats. His fever persisted and in November 1944 he became bedfast because of weakness and daily chills and fever. His temperature did not exceed 104.5° F. For the two weeks prior to admission he had a severe cough productive of one-half cup of thick sputum. The sputum varied from rusty to yellowish-green in color and was foul to the taste. Dyspnea and orthopnea were present. There had been considerable weight loss. During the last two weeks before his admission to the hospital he had been given one gram of some sulfonamide every four hours.

Physical examination at the time of admission revealed the following significant findings: he was acutely ill and orthopneic; the nasal mucous membrane was mildly injected and there was a small amount of exudate on the right tonsil; there was generalized lymphadenopathy of slight degree without any associated tenderness, fixation or matting of the nodes; there was evidence of consolidation in the right mid-lung field; there was tenderness in the region of the gastrectomy scar; the testes were atrophic; rectal examination revealed the same extra-rectal mass previously noted. Roentgen-rays revealed extensive consolidation in the base of the right upper lobe, non-visualization of the gall-bladder, and profound deformity of the upper one-half of the stomach, nature indeterminate. Urinalysis was negative. Hemoglobin was 13.8 gm. The total red blood cell count, total white blood cell count and differential count were normal. The sputum was negative for acid-fast bacilli on concentrate and culture.

Throughout this admission his temperature was septic in type, varying from 93.4° F. to 105° F. Penicillin in dosage of 20,000 units every three hours was administered intramuscularly from Dec. 13, 1944 through Dec. 23, 1944. Bronchoscopy on Dec. 22, 1944 was negative. He went into shock on Dec. 24, 1944 and died seven hours later. Penicillin had no effect on the fever or the clinical appearance of the patient. He received a total of 1,580,000 units of penicillin.

At autopsy, histoplasmosis was found involving the right lung, spleen, liver, kidney, and bone marrow. There was a severe chronic peri-esophagitis with partial obstruction of the lower esophagus. After autopsy the biopsy taken at sigmoidoscopy on June 7, 1943 was reviewed and a few Histoplasma were found in the submucosal granulomatous focus. Figure 1 shows the organisms in a section.

F. F., a 30 year old white female, was first admitted to the University Hospital on Sept. 11, 1944 complaining of a painful right hip of one month's duration. In July 1943 she suddenly developed a soft, tender, red, hot swelling in her right lower quadrant. There were no constitutional manifestations. About five days later an appendectomy was performed. Three months pregnant at the time, on the third postoperative day she aborted. This was followed by puerperal sepsis and she was severely ill for several months. She was given sulfonamides during this period. Recovery was apparently complete and she returned to work as an electroplater. In October 1943 she developed a dry non-productive cough which persisted until February 1944. In November 1943 she noted a gradually progressive swelling in the right cervical region which enlarged to the size of a hen's egg. This was hot, painful, tender, and reddish-purple in color. It was accompanied by afternoon fever as high as 102° F. and occasional night sweats. Daily fever persisted from this date until admission to the University Hospital in September 1944. The mass in the neck was incised and drained a yellowish watery fluid for eight months before healing. In January 1944, splenomegaly and hepatomegaly were noted for the first time. In the same month a gradually enlarging swelling was noted on the right wrist. This manifested the same characteristics as the previous swelling in the neck. Jaundice was present throughout April 1944 and her liver was exquisitely tender. The tumor on the right wrist was incised in May 1944 and discharged a sanguino-purulent fluid. Healing was delayed. During May she was given 1,000,000 units of penicillin intramuscularly in divided doses at two hour intervals. Chest roentgenograms at the local

hospital revealed slight prominence of the right hilar shadows. Two weeks after the course of penicillin was completed tumefactions appeared on her forehead, two on her right leg, and two on her left leg. These all drained and superficially healed with the exception of the two on the right leg which were still draining at the time of admission to University Hospital. On September 1, 1944, she again developed a mild cough which was productive of small amounts of yellowish sputum. Weight loss was gradual, amounting to 44 pounds. Her past history was not contributory to the present illness. She had worked as a housewife and electroplater; she had also been engaged in the manufacture of mat landing strips for airplanes.

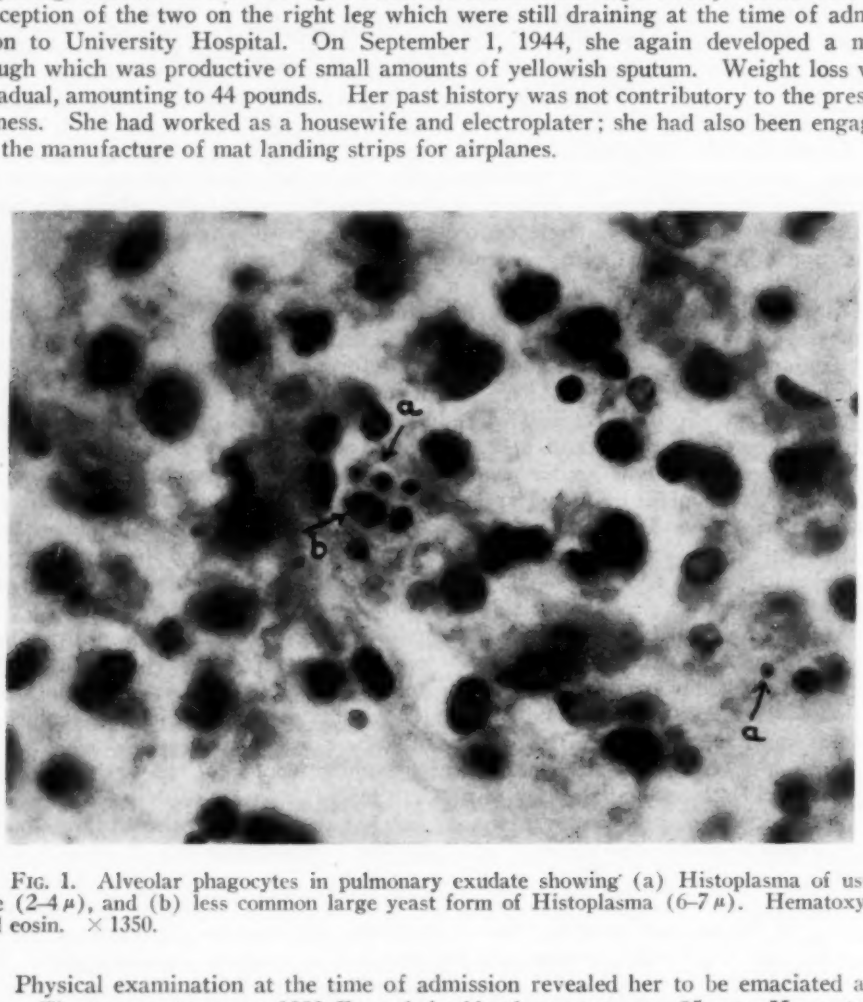

FIG. 1. Alveolar phagocytes in pulmonary exudate showing (a) Histoplasma of usual size (2–4 μ), and (b) less common large yeast form of Histoplasma (6–7 μ). Hematoxylin and eosin. × 1350.

Physical examination at the time of admission revealed her to be emaciated and pale. The temperature was 100° F., and the blood pressure was 95 mm. Hg systolic and 60 mm. diastolic. There were two draining granulomatous lesions on the right calf, one on the left calf and one on the left thigh. Healed lesions were seen on the wrist and the right side of the neck. There was a tender fluctuant nodular lesion on the forehead with a brownish-purple discoloration. The healed lesions were roughly linear with a hypertrophic pigmented type of scar. There was no generalized lymphadenopathy. The spleen was palpable. The liver was palpated 3 cm. below the right costal margin in the midclavicular line and was slightly tender. There was pronounced tenderness over the right hip with associated muscle spasm. Chest roentgenograms revealed right hilar adenopathy and patchy pneumonitis of the right lung, which gradually regressed during the next two months without entirely disappearing. Roentgenograms of the pelvis, lower extremities, esophagus, stomach, and small bowel were negative.

The total red blood cell count was 3,900,000. The hemoglobin was 10.9 gm. The total white blood cell count was 4,850. Differential count was essentially normal. Sternal and splenic aspiration revealed no Histoplasma. Twenty-five ml. of venous blood were centrifuged on Oct. 13, 1944 and again on Feb. 24, 1945. No Histoplasma were found in films made from the buffy coat. Urinalysis was negative. Bromsulfalein liver function test showed 40 per cent retention at 30 minutes. The Mantoux test with 1: 10,000 O.T. was positive. Intracutaneous histoplasmin gave a 3 by 2 cm. induration in 48 hours and a 5 by 3 cm. area in 72 hours. Broth control was negative. The blood serologic reaction was negative. Sputum culture for fungi on Sept. 15, 1944 revealed only a slight growth of monilia. Cultures taken from a skin ulcer were negative for fungi. Blood cultures taken on Oct. 5, 1944 and Nov. 9, 1944 were negative for Histoplasma, aerobes, and anaerobes. Stool culture for the typhoid-paratyphoid-dysentery group and Histoplasma was negative on Nov. 14, 1944.

Biopsy from a leg ulcer on Sept. 13, 1944 was reported as showing a "chronic infective granuloma which cannot be diagnosed on histological characteristics alone. No organisms are found on routine preparation." A biopsy from the forehead lesion on Sept. 19, 1944 was reported as: "This is a chronic infective granuloma. It does not have the characteristics of blastomycosis since it produces epithelioid tissue around caseous centers. Staining for tubercle bacilli on the previous specimen from this patient has given only negative results. If syphilis has been excluded by history and serological test, histoplasmosis seems to us to be the most probable diagnosis, but as yet we have failed to demonstrate any organisms." A biopsy taken from an ulcer of the left thigh on Sept. 29, 1944 was reported similar to the biopsy from the forehead.

Throughout this period of hospitalization she ran a low grade fever with occasional peaks to as high as 103.8° F.

She was given ultra-violet light to the skin lesions on four occasions with noticeable improvement. She gained 14 pounds in weight and was discharged on Nov. 22, 1944.

She was seen for check-up examination in the medical clinic on Jan. 22, 1945. At that time she stated that she was feeling quite well, although low-grade fever had continued. She had remained at strict bed rest. The skin lesions appeared to be quite well healed, leaving deep purplish indurated scars. The liver and spleen were still enlarged. Chest roentgenogram on this date revealed linear areas of increased density in the right lower lung, principally in the right middle lobe, showing increase in discreteness since November 1944.

Shortly after returning home from the clinic visit of Jan. 22, 1945 she became much worse. Her temperature at times rose as high as 104° F. and her cough became more severe. For several weeks she raised small amounts of yellowish sputum daily. Chest pain was present with dyspnea for the two weeks prior to her second admission on Feb. 24, 1945. For several weeks she had had periods of nocturnal delirium.

On her second admission the anterior cervical lymph nodes were moderately enlarged. Mild clubbing of the fingers was noted. During her second hospitalization her temperature varied from 96° F. to 104.6° F. taken rectally. She was irrational and comatose most of the time, although at times she was perfectly lucid. Chest roentgenogram on Feb. 24, 1945 revealed widely disseminated parenchymal disease in both lungs developing for the most part in the past month. Direct examination of the sputum on Feb. 25, 1945 revealed a rare intra-cellular *Histoplasma capsulatum*. The sputum was also positive for type 6 Pneumococci and *Hemophilus influenzae*. A small sputum sample was specially treated and injected into guinea pigs. This is discussed together with the bacteriological studies made at autopsy.

It was planned to treat her with stilbamidine but, since she had received penicillin in May, it was decided to note the effects of large doses of penicillin. She was given 20,000 units of penicillin intramuscularly every hour from Feb. 27, 1945 until her

death on March 3, 1945. She was also given 20 ml. of adrenal cortical extract on three of these days. No perceptible effect of penicillin in this dosage was noted other than a regression in the size of the liver and spleen, which could not be attributed definitely to penicillin. She received a total of 1,800,000 units of penicillin during this admission.

At autopsy the essential pathological diagnoses were: "Histoplasmosis. Mixed infection with tuberculosis (both *Histoplasma capsulatum* and tubercle bacilli demonstrated). Bilateral confluent necrotizing pneumonitis. Extensive granulomatous peritonitis with multiple adhesions, tubercle-like lesions, and abscesses. Extensive liquefy-

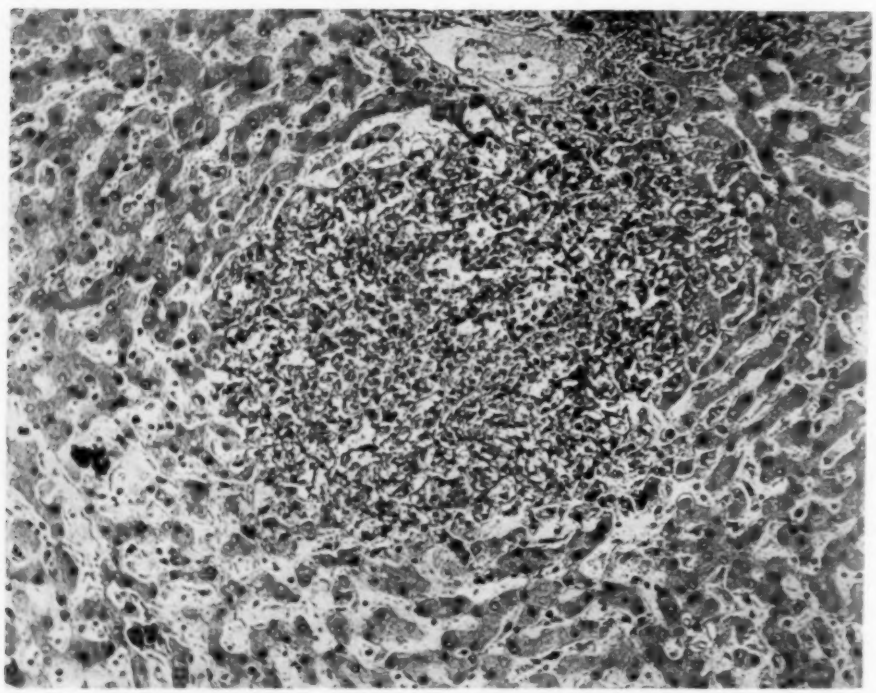

FIG. 2. Granulomatous focus of histoplasmosis in liver. Note the practical absence of tissue reaction to the area of necrosis. Histoplasma are present at the periphery of the granuloma. Hematoxylin and eosin. × 150.

ing lesions in liver and abdominal lymph nodes. Miliary lesions in brain, spleen, liver, thyroid, capsule of the pituitary body, adrenals, kidneys, and urinary bladder. Chronic granulomatous salpingitis. Chronic adhesive pleuritis. Old fibrocalcareous tuberculosis of the right upper pulmonary lobe. Healed and healing lesions of the skin." The appendix was surgically absent. One area in the large intestine showed a tiny ulceration communicating with a subserosal structure containing much thick, creamy exudate. A single inflammatory lesion in brain sections had a necrotic center in which there were small bodies indistinguishable from Histoplasma in routine stains. In the lungs *Histoplasma capsulatum* was present in enormous numbers in granulomatous foci. The interior of a venous thrombus was nearly filled with Histoplasma. Very large numbers of this organism were found in the spleen. In the large intestine there were encapsulating caseous foci on and beneath the serosa, some of which were very

rich in Histoplasma. In the bone marrow there were occasional small foci of necrosis which resembled primary tuberculous necrotic foci, but Histoplasma were found in these lesions. In the oviducts a chronic granulomatous salpingitis and peri-salpingitis were present. *Histoplasma capsulatum* was present, but the pathologist believed that this probably represented a mixed infection. Tubercle bacilli were demonstrated in some of the miliary granulomatous foci in the liver. Figure 2 shows a granuloma of the liver due to histoplasmosis.

Numerous cultures were made from various tissues at autopsy. Some of these were positive for *Histoplasma capsulatum* and *Mycobacterium tuberculosis*. Of especial interest are the antemortem sputum sample and several bits of postmortem tissue. Both the sputum sample and the ground autopsy tissue were treated with penicillin in an amount to make the total concentration in each case four units per ml. These materials were then inoculated into guinea pigs. The guinea pigs were autopsied and revealed infection with *Histoplasma capsulatum*. The guinea pig inoculated with ground postmortem tissue also exhibited tuberculosis.

Discussion

Neither of the two cases reported received penicillin in very large total dosage nor was it administered for a considerable length of time. It is true that the second patient received 480,000 units per day, but only for four days. It may, of course, be argued that the relatively large doses of penicillin administered during the second course of treatment in the latter case carry no greater weight in regard to the value of penicillin in histoplasmosis than does the small dosage employed in the first case. This would be true if an effective dose level were attained by the dosage used in the first case inasmuch as there is probably no real advantage in exceeding the level of effective dosage. However, at the time of treatment of both cases no data were at hand to suggest what the minimum effective level might be. It was hoped that 20,000 units of penicillin every hour would attain an effective level, if such is practicably attainable with penicillin. There is no question but that the duration of this dose level, whether effective or not, was altogether too short.

It is obvious from the pathology of histoplasmosis that no great amelioration of the disease can be anticipated in a period of a few days. However, one would expect an initial rapid decrease in the number of organisms to occur if the organism is susceptible to the concentration of penicillin present. The ready growth of Histoplasma from autopsy material and the abundance of normal appearing organisms in this material suggest that an effective level was not reached or that the organism was entirely insensitive to penicillin. Penicillin, in the concentration of four units per ml., was ineffectual in preventing the growth of Histoplasma when inoculated into guinea pigs. There is no assurance that a significant level of penicillin was maintained for an adequate length of time after this material was injected. It may be significant that the animals so inoculated were protected from the type 6 Pneumococci and the *Hemophilus influenzae* which had killed other guinea pigs and mice in less than 24 hours.

In vitro susceptibility studies with Histoplasma suggest that this organism is not inhibited by a concentration of 10 units of penicillin per ml. of broth. Susceptibility studies with other chemotherapeutic agents are in progress, but this work is not yet completed.

Conclusions

Two cases of histoplasmosis treated with penicillin over a brief interval of time showed no response to this treatment.

Bacteriological studies, at present incomplete, suggest that *Histoplasma capsulatum* is not susceptible to penicillin in concentrations clinically attainable.

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DEATH DUE TO ADMINISTRATION OF TYPHUS VACCINE*

By Harold Rifkin,† Major, M.C., A.U.S., *Brooklyn, N. Y.*

A recent editorial note in The United States Army Medical Bulletin states that a number of severe reactions due to typhus vaccine have been reported to the Surgeon General's Office, but that the number is negligible in comparison to the number of doses of egg vaccine administered. We have had occasion to observe all autopsied material in a South Pacific base. Only one case has come to autopsy as a result of typhus vaccine administration. Roth [2] has recently reviewed 32 cases of reactions to typhus vaccine. These reactions have been divided into two types. The first group consists chiefly of a constitutional reaction which is explained on the basis of foreign protein sensitivity. The second group is considered to be an allergic reaction to some constituent, possibly residual egg protein. The question of antigenicity of egg yolk is considered. One authority [3] mentions that sensitization to egg yolk has been reported but its actual existence is doubtful. Recent unpublished observations [4] made in the Division of Virus and Rickettsial Diseases, Army Medical Center, have revealed that egg yolk is antigenic and that sensitization to egg yolk does occur. We have recently had occasion to autopsy a young soldier who apparently was egg sensitive and had been given 1 c.c. of typhus vaccine as a prophylactic measure.

Case Report

A 24 year old white male soldier had been given 1.0 c.c. of typhus vaccine subcutaneously. Eight minutes following the administration of vaccine, he complained of severe difficulty in breathing. His respirations became shallow and irregular. There developed an extensive cyanosis of his entire body. Pulse was 140 per minute; blood pressure was lowered to 80 mm. Hg systolic and 40 mm. diastolic. Five minutes following this acute onset, the patient went into sudden and deep coma. Irregular spasmodic and convulsive movements of the lower extremities developed. Twelve minutes later all respirations and pulse had ceased, despite artificial respiration and administration of epinephrine. The patient's previous immunization record is noted in table 1.

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† At present with the Dept. of Medicine, Montefiore Hospital, Gun Hill Road, New York City.

TABLE I

Vaccine	Dose	Method	Date	Reaction
Smallpox		Scratch	12/ 9/42	Immune reaction
Typhoid:				
1st Injection	0.5 c.c.	Subcutaneous	12/16/42	Headache, malaise, slight generalized pruritus, developing 20 minutes following injection and persisting for six hours
2d Injection	1.0 c.c.	Subcutaneous	12/23/42	
3d Injection	1.0 c.c.	Subcutaneous	12/30/42	
Typhoid (Stimulating injection)	0.5 c.c.	Subcutaneous	12/20/43	Slight malaise
Tetanus:				
1st Injection	1.0 c.c.	Subcutaneous	1/23/43	Slight malaise and headache, persisting for four hours following injection
2d Injection	1.0 c.c.	Subcutaneous	2/14/43	
3d Injection	1.0 c.c.	Subcutaneous	3/ 7/43	
Typhus	1.0 c.c.	Subcutaneous	10/20/44	Symptoms and signs of anaphylactic shock with resultant death

This revealed no previous administration of typhus vaccine. A review of the patient's past medical history revealed no severe illnesses. He had been on prophylactic atabrine 0.7 gm. per week for one year. He had never been hospitalized for malaria. A note is made in the out-patient record that "The patient gives a history of nausea, vomiting, and lassitude, invariably following ingestion of eggs, both raw and cooked. Almost constantly, smells such as cake and pie are followed by a feeling of fullness and nausea." No attempt, however, had apparently been made prior to typhus vaccine administration, to confirm a diagnosis of egg sensitivity by intradermal injection of diluted vaccine.

Necropsy

Gross Findings: Autopsy was performed two hours following death. The body was that of a well-developed, well-nourished young white male, weighing 165 pounds and measuring 169 cm. in length. A distinct yellow-brown pigmentation of the skin was noted over the entire body. The sclera of both eyes revealed a similar yellow-brown pigmentation. The pleural and peritoneal cavities revealed 8 c.c. and 20 c.c. of yellow-amber fluid respectively; 5 c.c. of light yellow fluid were noted in the pericardial cavity. Numerous petechial hemorrhages were noted on the posterior surface of the base of the left ventricle. These were superficially located, circular in outline, and measured 3 to 5 mm. in diameter. There was diffuse dilatation of the right auricle and ventricle, denoted by flattening and increased interspaces between the trabeculae carneae and pectinate muscles. The wall of the right and left ventricles measured 4 mm. and 7.5 mm., respectively. The right and left lungs weighed 950 and 850 gm., respectively. Each lung revealed such extensive emphysematous-like inflation that they completely filled their respective pleural cavities. Distinct subpleural blebs were noted in the right and left upper lobes. Tiny petechial hemorrhages measuring 3 to 5 mm. in diameter were noted throughout all lobes. The lung parenchyma was gray-blue, crepitant, elastic, and feathery in consistency. On section, no areas of consolidation were noted. The lumina of the bronchi and bronchioles were not dilated. A thin serous fluid was noted within the lumen of the small bronchi in the region of the right and left lower lobes. The mucous membrane was smooth, pink-red in color, and free of hemorrhage, ulceration or an endo-bronchial lesion. The

vessels revealed no thrombi or emboli. The lymph nodes were not enlarged. Except for moderate congestion of the liver, spleen, kidney, and pancreas, no other remarkable features were noted.

Microscopic Findings: The most prominent findings were noted throughout all sections of the right and left lung. The alveoli were enlarged four to five times their usual size. The alveolar walls were stretched so that they appeared as thin, irregular, wavy hair lines (figure 1). Communication between alveoli existed as a result of rup-

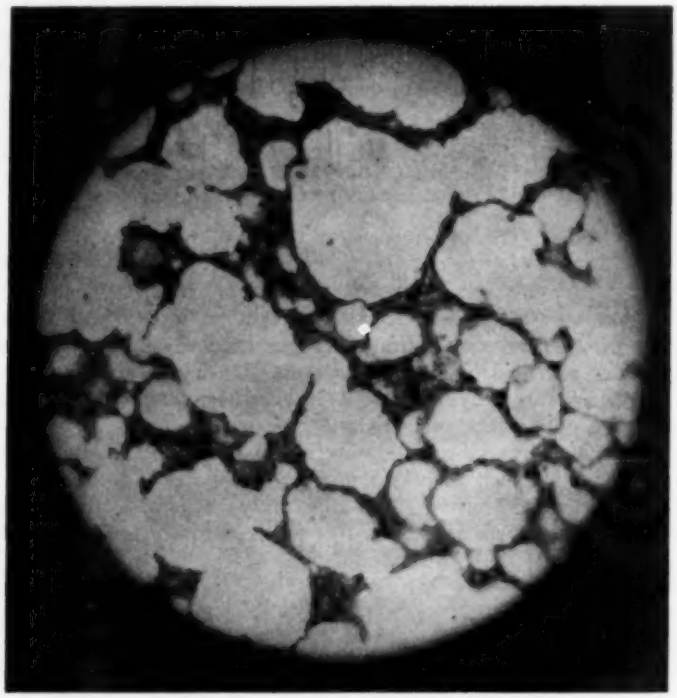

FIG. 1. Section through left upper lobe. Note the intense emphysema throughout. Hematoxylin and eosin. × 500.

ture of alveolar septa. No exudate was present within the alveoli. The capillaries were congested. In a number of focal areas, diapedesis of red blood cells into the inter-lobular septa was seen. Clumps of mononuclear histiocytes, containing fine, brown amorphous granular pigment were present with the large alveoli. Lining the small bronchi and bronchioles was a hyperplastic and stratified columnar epithelium. This epithelium projected into the lumen in an irregular fashion, so that it assumed a distinct scalloped appearance. The lumen itself was not dilated. It contained a thin pink-staining exudate which was infiltrated by small aggregates of round cells and eosinophilic leukocytes (figure 2). A similar eosinophilic infiltration was noted throughout the mucosa and submucosa producing moderate thickening of the small bronchial and bronchiolar walls (figure 3). The mucosal vessels were moderately congested. No fragmentation and splitting of the elastic fibers were noted. The muscle fibers and cartilage plates were intact. Sections from the abdominal viscera revealed a moderate congestion throughout. No other remarkable features were noted. Microscopic examination of multiple sections of the brain was normal.

Comment

Death here appears to have been essentially due to anaphylactic shock secondary to typhus vaccine injection. The patient had apparently been known to be egg sensitive. It is suggested, therefore, that this reaction was allergic in nature, and the antigenic substance appears to have been egg protein, possibly albumin or egg yolk. It is of interest to theorize whether death could have been avoided if confirmation of egg sensitivity had been made by intradermal injection of diluted vaccine.

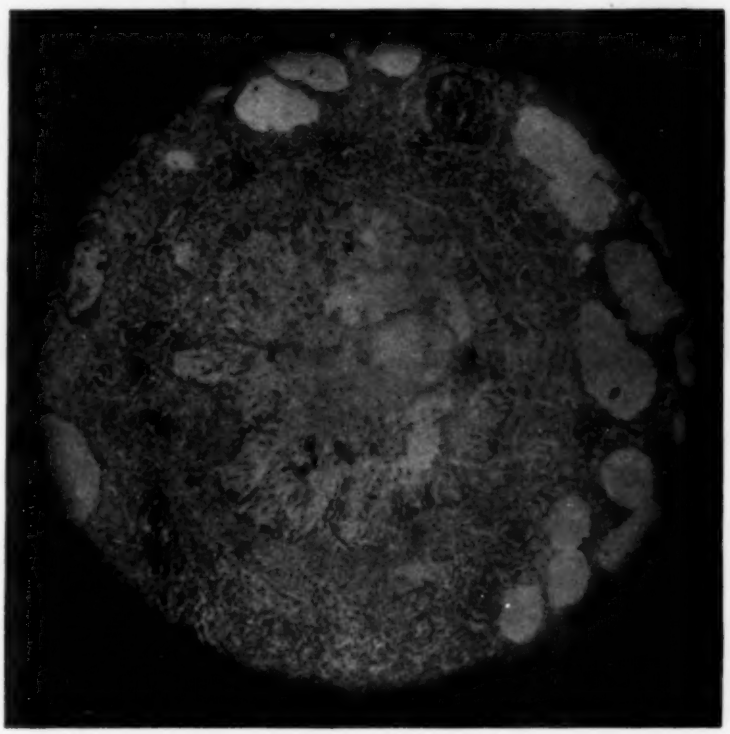

FIG. 2. Section through small bronchus, right upper lobe. Note the scalloping of the epithelial lining, the eosin staining luminal exudate with eosinophilic infiltration, and the thickening of the bronchial wall by eosinophilic and round cell infiltration. Hematoxylin and eosin. × 350.

The predominating findings are noted in the respiratory system. These consisted chiefly of a severe bilateral and diffuse emphysema, a striking eosinophilia in a thin eosin-staining luminal exudate, and eosinophilic infiltration of the walls of the small bronchi and bronchioles. The morphologic findings suggest the bronchial passages as the shock organ. A comparison with acute anaphylactic shock in guinea pigs is immediately drawn. It may well be that the pulmonary findings were the result of tetanic contraction of the bronchial musculature with eventual asphyxia.

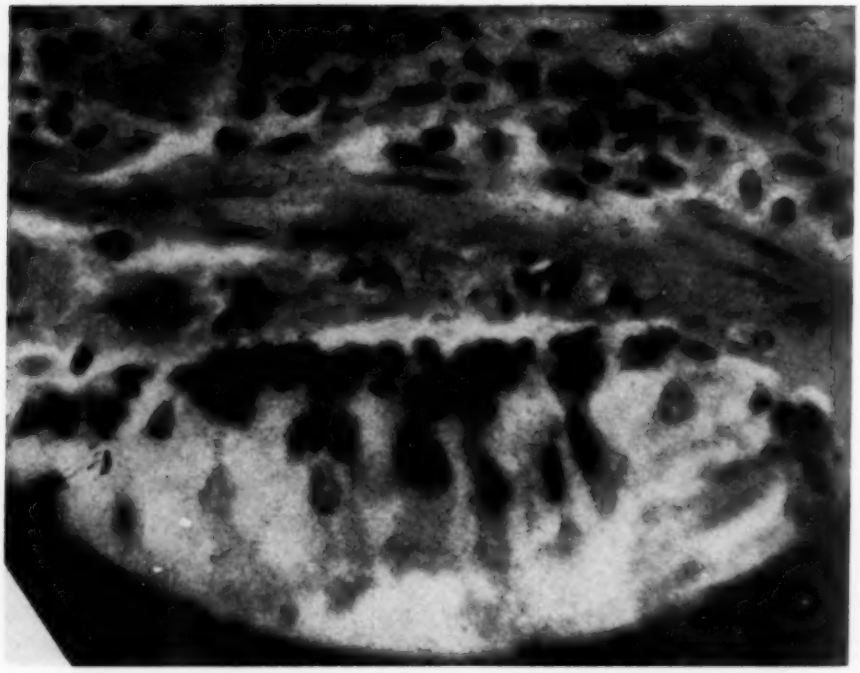

FIG. 3. Section through wall of small bronchus, right upper lobe. Note the hyperplastic columnar epithelium, and cellular infiltration of the mucosa. Hematoxylin and eosin. × 650.

CONCLUSIONS

1. A case is reported of an egg-sensitive soldier in whom a typhus vaccine reaction developed, with eventual death.

2. It is believed that the shock organ here was the respiratory passages, and that the anatomical findings are consistent with those noted in acute anaphylactic shock in guinea pigs.

3. It is suggested that all patients who are to receive typhus or other egg-yolk vaccine, who are suspected of being egg sensitive, be given an intradermal injection of diluted vaccine to confirm such a suspicion.

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REGIONAL ILEITIS INVOLVING THE ILEUM, CECUM, ASCENDING COLON. AND TRANSVERSE COLON *

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Since 1932 when Crohn, Ginzburg, and Oppenheimer [1] first published their paper on 13 cases showing necrotizing cicatricial inflammation of the terminal ileum, many reports have appeared in the literature on the subject of granulomatous ileocolitis, commonly called "regional ileitis." Reports of cases showing widespread involvement of the cecum, ascending and transverse colon, as well as of the terminal ileum are uncommon. Bockus and his associates report 21 cases of regional ileocolitis,[2] seven of which showed involvement of terminal ileum and colon proximal to the sigmoid. Ravdin and Johnston [3] in a summary of the literature tabulate 10 instances in a series of 393 cases in which the disease process is entirely confined to the cecum.

The disease was originally believed to involve principally the terminal ileum in a chronic, granulomatous process and was characterized clinically by the presence of anemia, diarrhea, abdominal pain, low grade fever, and a mass in the right lower quadrant. Later it was observed that other segments of bowel could be involved by a similar process, particularly the upper part of the ileum, the lower jejunum and the proximal portion of the colon. In many cases, areas of pathologic involvement alternated with normal bowel for a variable distance. Some authors have attempted to distinguish between "regional ileitis" and "regional colitis" as separate entities, but the pathologic changes are so specifically similar that the disease is undoubtedly one and the same irrespective of the part of the intestine attacked. The case reported here illustrates this fact particularly well since the major portion of the disease involved the cecum, ascending colon and transverse colon, and extended in lesser degree to the terminal ileum and the distal portion of the transverse colon.

Many authors believe that the disease should be called granulomatous ileocolitis because of the characteristic granulomatous lesion in the wall of the intestine, which has often been described and which presents a distinctive pathologic picture. Its marked histologic resemblance to tuberculosis has often been noted; however, cultures, smears, and guinea pig inoculations of stool specimens and of operative specimens have consistently failed to reveal any evidence of tubercle bacilli.

No definite etiological factors have been determined, although acute bacillary dysentery has been suspected of having some etiological relationship. Following the epidemic of acute bacillary dysentery in Jersey City, Felsen [4] reported 29 cases of acute inflammation of the distal ileum as an early complication, and observed at operation that the ileum was red, edematous and thickened. Bacteriologic examinations were negative for organisms of the dysentery group, although many cases had a history suggestive of a previous bacillary dysentery. Some cases, as well as the case reported here, have shown positive serum agglutination tests for the dysentery organisms in high dilutions. It may be conjectured from

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Felsen's observations that the bacillus dysentery is the primary causative agent in some cases of regional ileocolitis. Chronic, ulcerative colitis has also been suspected of having some relationship to regional ileocolitis, although the pathological picture is not at all similar. Crohn believes that chronic ulcerative colitis and chronic regional ileitis may represent different residual phases of earlier dysentery infection, but this belief lacks clinical, bacteriologic, or pathologic evidence.

The clinical diagnosis of granulomatous ileocolitis is based primarily on roentgenological findings. These vary according to the stage in which the disease is discovered. In the very early stage nothing more than irritability, localized spasm and hypermotility of the involved segment (usually the terminal ileum) may be seen. As the disease progresses, this portion of the intestine becomes smooth, thickened and contracted, with narrowing of the lumen producing the typical "string sign." There is obliteration of the normal mucosal pattern and on spot pressure film ulceration of the mucosa of the involved segment may be demonstrated. The margins of the diseased portion are slightly fuzzy and irregular as a result of ulceration. In the later stages it is not uncommon to have marked constriction sufficient to cause obstruction associated with dilatation of the intestine proximal to the lesion, accompanied by the development of fistula. Roentgenologically, the extent of involvement is often sharply demarcated. It is the experience of many roentgenologists that a barium meal will demonstrate findings of greater value in this disease than will the barium enema. However, no case should be subjected to operation without a barium enema. Examination of postoperative or autopsy specimens, however, usually reveals macroscopic and microscopic evidence of diseased bowel extending beyond the point of demarcation.

From the roentgenologic standpoint, the differential diagnosis usually limits itself to regional ileitis and ileocecal tuberculosis. Primary enterocolic tuberculosis is relatively rare. In the absence of pulmonary tuberculosis and with the inability to recover acid fast organisms from the stool, intestinal tuberculosis can usually be excluded, although an occasional case cannot be distinguished from regional ileitis, except at operation. Neoplasm, appendiceal abscess and Meckel's diverticulitis should be considered, but the history and the roentgen-ray findings are usually sufficient to exclude these.

Clinically, the early symptoms of regional ileitis closely resemble those of acute appendicitis. This is illustrated by the fact that at least 50 per cent of the reported cases of regional ileitis have a history of a previous appendectomy. In the later stages of the disease, however, the resemblance to appendicitis is less striking. Amebic colitis, chronic bacillary dysentery and ulcerative colitis must be considered in the differential diagnosis. Amebic colitis usually will show typical small discrete punched-out ulcers in the lower bowel with pus and blood in the stool, and the amebae may often be recovered from a warm stool specimen. Ulcerative colitis can usually be diagnosed by roentgen-ray and the sigmoidoscopic examination. The diagnosis of chronic bacillary dysentery depends on the isolation of the specific organism from the stool, and rising serial serum agglutination titers.

It is the general consensus of opinion that the only satisfactory treatment of granulomatous ileocolitis at the present time is surgical, although recently there is a growing feeling that some cases, especially those showing minimal involve-

ment, may respond to medical treatment. Maintenance of an optimum nutritional status with periodic exposures to ultraviolet ray are helpful. As Marshall [5] points out, there is considerable difference of opinion as to the time and type of operation that may be indicated. There is general agreement that all of the diseased bowel and the diseased mesenteric glands must be removed if a satisfactory result is to be obtained. In this connection, it is important for the surgeon to remember that more than one portion of the bowel may be involved, so that in all cases a complete exploration of the intestinal tract from the duodenum to the rectum should be done. The type of operation which is advised is a wide resection of the affected bowel with its mesentery with a primary end to end or side to side anastomosis. Marshall prefers the two stage Mikulicz type of operation, particularly in the presence of secondary infection. When there is a secondary abscess present, it may be necessary to drain the abscess first and to carry out the necessary resection at a later date. The immediate results of this procedure have been very variable. Even in the best hands, there has been at least a 10 per cent recurrence after complete resection of the diseased bowel. The presence of simple diarrhea for many months after operation need not, however, be considered as evidence of recurrence for it occurs in many patients who otherwise show no evidence of disease, have gained weight, feel well, and who show no roentgenological changes.

The case report below is given in considerable detail, because of the unusually widespread involvement of his intestinal tract, and because the patient, closely followed in Army hospitals for over a year, illustrates very graphically the classical picture of the onset and progress of this disease, with all its diagnostic and therapeutic trials and pitfalls.

Case Report

Male, white, age 22, admitted to Fletcher General Hospital, August 10, 1943, with a diagnosis of diarrhea, acute, severe, type and cause undetermined. He had always enjoyed good health until February 1943, eight months after entering active military service, when he began to have diarrhea of three to five watery bowel movements daily, associated with right lower quadrant cramps, weight loss and fever. The pain occurred about 20 to 30 minutes after eating and was usually relieved shortly after his bowels moved. He reported on sick call on numerous occasions, but was not hospitalized owing to the fact that the diarrhea was not very severe. In April 1943, he began to have increased diarrhea and abdominal cramps and after two weeks without relief was admitted to the local station hospital, where with bland diet and rest he improved in two weeks and was discharged back to duty.

After two days on duty, his pain and diarrhea again recurred and he was readmitted to the hospital May 12, 1943. At this time more extensive studies were done. He was found to be running a low grade fever up to 101° F. Stool examinations showed many red blood and pus cells, but no gross pus or blood. No specific organisms or amebae were found in the stool cultures, but blood agglutination titers for Flexner Y and Shiga organisms were positive in 1 to 320 dilutions on two occasions. Sigmoidoscopy was performed twice and showed an edematous, red mucosa which bled easily, but no definite ulceration. Roentgen-rays of the upper intestinal tract were negative except for a mildly irritable duodenal bulb. Three barium enemas were performed. The result of an enema on May 18, 1943, showed no gross filling defect or obstruction in the large bowel. The barium in the descendens had a peculiar granular appearance suggesting the possibility of superficial ulceration or edema of the mucosa.

The sigmoid was definitely tender to palpation. A repeat barium enema on July 5, 1943, six weeks later, showed no gross filling defects of the large bowel. The mucosal pattern of the transverse colon and descendens was slightly irregular and the cecum was spastic. Study of the ingested meal showed the head of the barium column to have reached the descendens in four hours. The distal 10 cm. of the ileum and the cecum were very spastic and tender to palpation. These findings were considered compatible with regional enteritis. A third barium enema on July 20, two weeks later, disclosed no evidence of gross filling defect. The entire large bowel and especially the cecum was quite irritable. Owing to this irritability the cecum could not be properly filled at the time. The post evacuation film showed rather deep mucosal folds in the transverse colon, but was otherwise not unusual.

In retrospect, it would seem that on the basis of these findings, a diagnosis of regional ileocolitis involving the terminal ileum and the cecum and possibly other portions of the colon could have been made with considerable confidence. However, although the diagnosis was mentioned in a final summary, the evidence was not considered sufficient to make a positive diagnosis at that time. While in the hospital, the patient was treated with low residue diet, paregoric and kaomagma, and a course of sulfaguanidine without obtaining any marked improvement.

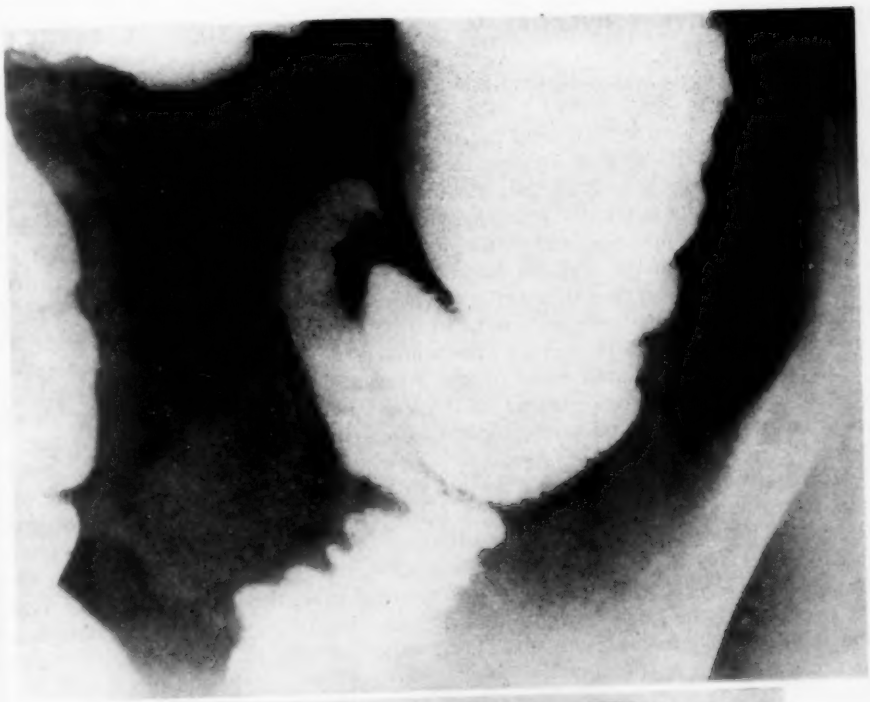
On July 22 the patient was transferred to another hospital. Here no additional information was obtained, except that the patient continued to run a low grade temperature, showed a persistent leukocytosis of about 11,000 white blood cells, and continued to have diarrhea and abdominal pain. The examining officers at this hospital were impressed with the patient's nervousness and anxiety, and considered the possibility of his diarrhea being of psychogenic origin associated with a vitamin deficiency. The patient was subsequently transferred to Fletcher General Hospital August 10, 1943.

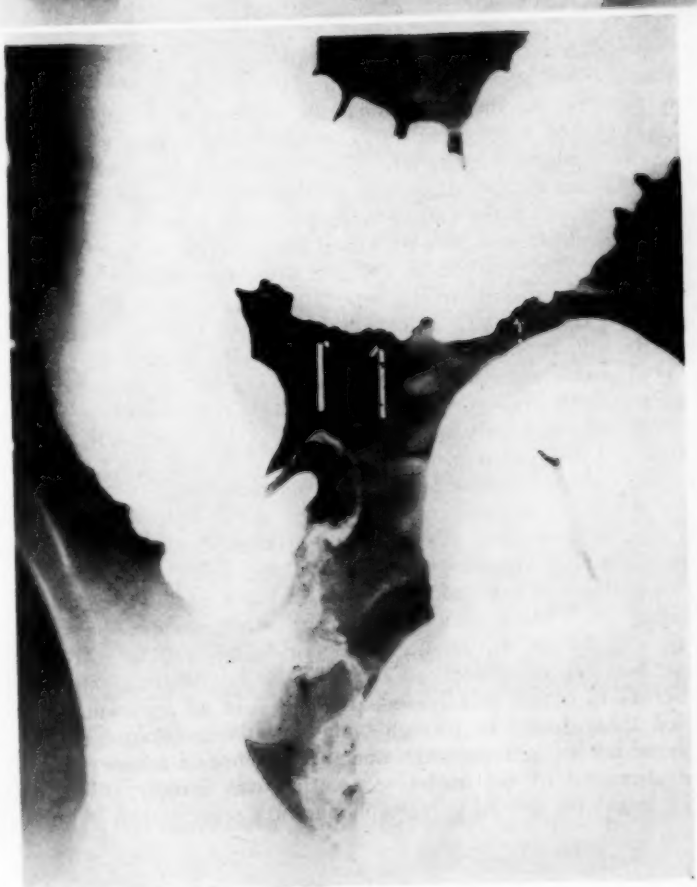
On admission to this hospital the medical consultant suspected, primarily, terminal granulomatous ileitis and secondarily ulcerative colitis because of the chronic diarrhea of six months' duration, low grade fever, loss of weight and the presence of a soft, palpable mass in the right lower quadrant. The previously described sigmoidoscopic findings were confirmed. A gastrointestinal roentgen-ray examination and barium enema were done on August 11 and repeated on August 17 for confirmation. The colon filled readily with the opaque enema and was normal down to the region of the cecum. The cecum distal to the ileocecal valve appeared somewhat conical in shape and its margin was somewhat irregular. The most significant finding was a very smooth tubular appearance of the distal eight centimeters of the ileum which was somewhat narrowed and showed loss of the normal mucosal pattern (figure 1). The impression was expressed that we were probably dealing with a non-specific ileitis showing involvement of the cecum. The five hour film of the gastrointestinal series showed similar changes in the terminal ileum. The fluoroscopic examination at the same time demonstrated irritability of the terminal ileum and cecum. The barium enema on August 17 disclosed that the distal ileum showed the same appearance as previously described and that fluoroscopically the cecum was irritable and slightly deformed (figure 2). On one of the films with the distal ileum almost empty, there was a definite distortion of the mucosal pattern. These changes were considered diagnostic of terminal ileitis involving approximately eight centimeters of the distal ileum and the cecum.

On the basis of these findings, the diagnosis of terminal ileitis with involvement of the cecum and ascending colon was established. Surgical consultation was re-

FIG. 1. (*above*) Progress meal discloses the smooth tubular appearance of the distal 8 cm. of the ileum, with loss of normal mucosal pattern.

FIG. 2. (*below*) Barium enema shows similar involvement of the terminal ileum, as in figure 1. Arrows indicate the saw-tooth appearance of the mucosa of the proximal transverse colon suggestive of ulcerative involvement.





quested, the diagnosis was confirmed and a wide resection of the ileum and ascending colon was advised.

Operation was performed by Lt. Col. O. E. Nadeau on August 23, 1943. The distal 10 or 12 centimeters of the terminal ileum, the cecum and the ascending colon were involved in an indurated inflammatory process typical of regional ileocolitis. A lesser degree of inflammation extended along the transverse colon to its mid portion and along the proximal portion of the ileum for about 12 inches, associated with marked enlargement of the regional mesenteric lymph nodes. A resection was carried out in which about 18 inches of ileum, the entire cecum and ascending colon and half of the transverse colon were removed. A direct primary anastomosis between the ileum and the remaining distal end of the transverse colon was performed.

The pathological examination of the operative specimen revealed the typical macroscopic and microscopic picture of regional ileocolitis. The following detailed description of the gross and microscopic findings illustrate the pathological basis of this disease.

Macroscopic. Specimen was a portion of large and small bowel consisting of 38 cm. of ileum and 42 cm. of ascending colon. There was considerable engorgement of the serosa throughout and a moderate number of small pin point size, white nodules studded the surface of the cecal peritoneum. Many large, discrete, firm lymph nodes were present in the mesentery especially in the region of the ileo-cecal valve. Longitudinal section of the large bowel revealed thickening of the wall due to fibrosis and edema with increase in consistency. There were multiple, small, pin head size superficial areas of erosion studding the colon mucosa extending to the distal end of the preparation, but present in larger numbers in the region of the cecum. There were many large superficial as well as deeper ulcerations ranging up to the size of a dime which had a thick wall, a red, smooth, granulating base, were of variable size and shape, and were often confluent. A moderate amount of exudate covered the floor which could be washed away readily. The ulcers were somewhat serpiginous and undermined in some places (figure 3). The ulcerations appeared to be as numerous in the distal end as in the proximal end of the resected bowel. The mucosal folds of the large bowel were coarse and spongy, thickened, thrown up and stood out very prominently. The sub-mucosa was thickened and scarred, especially in the region of the ileo-cecal valve. The mucosa of the ileum, in contrast to that of the ascending bowel, did not show any ulcerative changes, other than very rare, superficial, pin point size erosions. The characteristic change here was the marked, nodular, pebble-grain appearance of the mucosa and accompanying edema and thickening of the wall of the distal 7.0 cm. of small bowel. Proximal to this region no areas of ulceration, follicular hyperplasia, stenosis, or scarring were noted; the transverse folds were somewhat thicker but not strikingly so. The lymph nodes were soft, moist, red-brown on cross section and revealed no areas of caseation.

Microscopic. Many sections taken from old indurated, as well as comparatively young and fresh lesions from the colon revealed the basic pathologic change to consist of a chronic, inflammatory granulomatous tissue reaction characterized by focal accumulations of round, large and small monocytic cells, frequently surrounding a central core of epithelioid cells and often possessing a variable number of Langhans giant cells (figure 4). These granulomata were usually seen in the sub-mucous layer, but they were also present in the subserosal regions as well as infrequently between the muscle bundles. In many sections these foci were identical with tubercles in appearance, whereas in others this resemblance was not as apparent. Here the giant cells resembled those found in foreign body granuloma because of the absence of typical peripheral nuclear arrangement, and the presence of a lesser number and more disorderly arrangement of the nuclei. Caseation was usually absent and there appeared to be a larger number of polymorphonuclears present than in tubercle follicles.

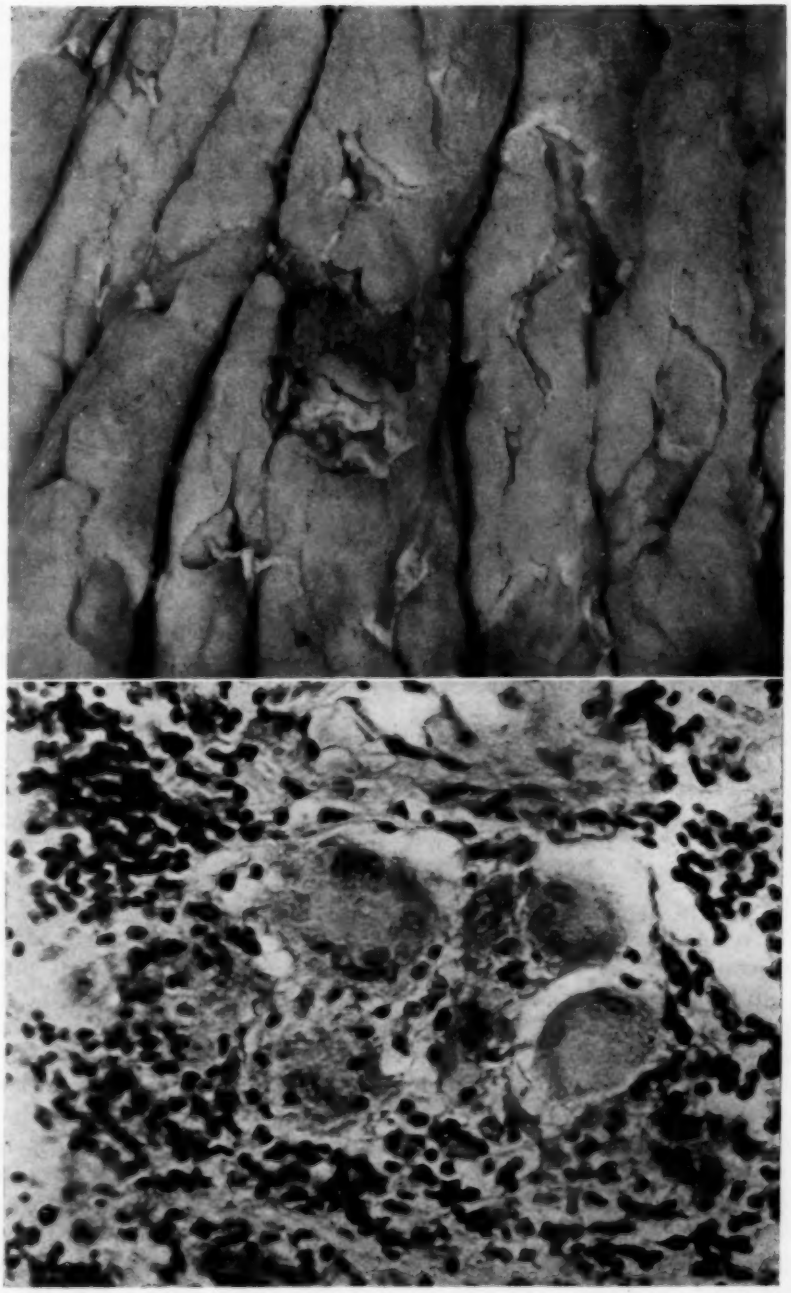


FIG. 3. (*above*) Gross specimen of cecum discloses serpiginous, flat, undermined, or punched-out ulcerations of the mucosa, possessing a dark discolored floor covered by fibrinopurulent exudate.

FIG. 4. (*below*) Photomicrograph discloses the granulomatous tissue reaction comprising epithelioid and Langhans' giant cells surrounded by many lymphocytes (560 ×).

The ulcerations usually revealed a floor composed of dense, chronic, unspecific granulation tissue which was quite vascular and which was composed of lymphocytes, fibrocytes, and plasma cells. Eosinophiles were present in variable numbers throughout. Sometimes these lesions were superficial and did not penetrate through the lamina propria, whereas in the older ulcers, penetration through the muscularis mucosa was seen with concomitant fibroblastic proliferation and scarring and dense granulation tissue (figure 5). The ulcers here were seen to be undermined, especially toward the distal end and sloping at the proximal end, in marked similarity to chronic peptic ulcers. Edema was very extensive in some places; in other areas, dense induration of the submucosa was the predominating change (figure 6). Sections through the ileum revealed no striking ulcerative or granulomatous changes, although there was thickening of the wall. Examination of the mesenteric lymph nodes disclosed a striking focal, tubercle-like granulomatous reaction in the peri-adenomatous tissues. Here the resemblance to tuberculosis was again very strong, but again, no caseation was noted and frequently but less often, the giant cells mimicked those seen in foreign body reactions. The lymph nodes revealed marked lymphoid hyperplasia, the follicles being large and numerous. The sinuses were swollen and filled with a coagulated albuminous exudate containing many large monocytic and plasma cells, while the reticulum cords were thickened and very prominent. In other nodes, the tissue seemed to be composed mainly of sheets of densely packed lymphocytes.

Stool examinations for tubercle bacilli by smear, culture, and guinea pig inoculation were consistently negative. Cultures of bowel surface and ulcers on EMB, and desoxycholate citrate revealed no organisms of the Salmonella or Shigella groups. The tissue reaction resembled that of tuberculosis but many points of difference existed. The giant cells were usually more like those seen in foreign body granulomata and caseation was consistently absent. Neutrophiles and round cells were seen in the epithelioid core in larger numbers than were usually present in tubercles. The inability to identify tubercle bacilli made it difficult to substantiate a diagnosis of tuberculosis. The pathologist thus was faced with the differential diagnosis between: (a) Regional colitis (the counterpart of regional ileitis or Crohn's disease) and (b) tuberculosis of the ascending bowel. It was felt that the former was the most likely diagnosis.

Discussion

The patient made an excellent recovery from his operation and during the next three months gained weight rapidly and felt and looked well. However, he still complained of infrequent diarrhea and abdominal cramps at times. A check-up barium enema on October 13 showed some irregularity of the mucosal pattern of the proximal 10 cm. of the transverse colon and of the extreme distal portion of the ileum (figure 7). The impression was that this indicated recurrence of a granulomatous and probably ulcerative process in the colon and possibly in the terminal ileum.

On November 24 the patient had an attack of sharp right sided abdominal pain and began to run an intermittent fever up to 103° and 104° F. In spite of bed rest and a course of sulfadiazine, followed by a course of sulfaguanidine treatment, the fever and abdominal symptoms continued, associated with considerable tenderness in the right lower abdomen. Another barium enema done on December 4 showed no change in the picture of the large bowel, but showed a coarsened and fuzzy mucosal pattern of the distal 12 to 15 cm. of the ileum. On December 21, the patient had an acute attack of pain in the lower right chest and shortly thereafter developed fluid in the right pleural cavity. He again began to run a high temperature, together with increased tenderness in the right

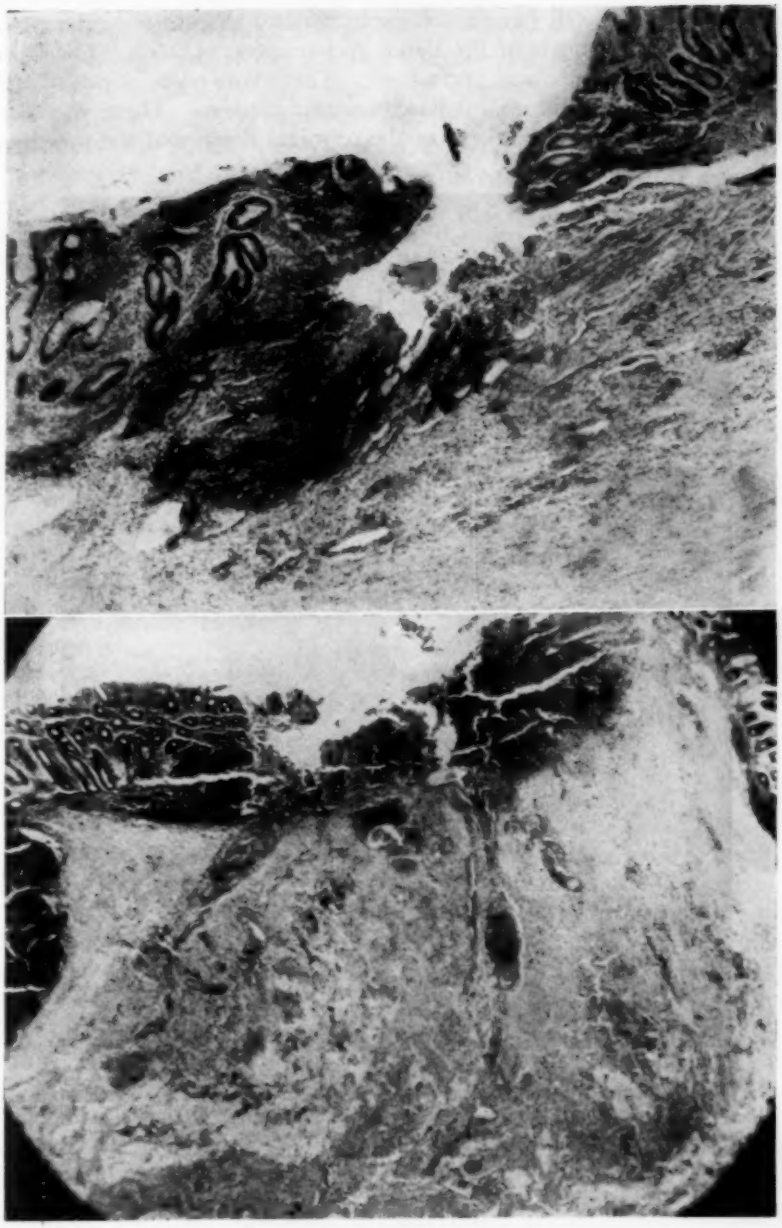


FIG. 5. (*above*) Photomicrograph demonstrates the penetrating funnel-shaped ulcer. It exhibits the characteristic undermining, granulomatous reaction and involvement of the submucosa (70 ×).

FIG. 6. (*below*) Photomicrograph of a chronic ulcer demonstrating marked induration and fibrosis of the submucosa (26 ×).

abdomen. Marked elevation of the right diaphragm was noticed and it was felt that the patient might well have a subdiaphragmatic abscess secondary to infection around the anastomosis of the ileum and transverse colon. On December 29, exploratory laparotomy was performed. There was no evidence of infection around the anastomosis and no subdiaphragmatic abscess. There was a moderate amount of induration and edema of the terminal ileum and the proximal por-

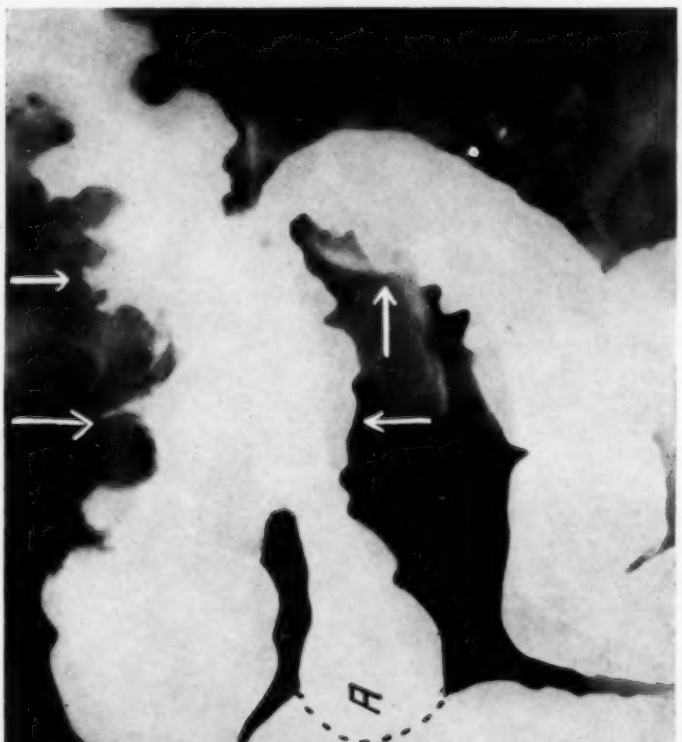


FIG. 7. Barium enema performed seven weeks after intestinal resection shows marked irregularity of the mucosal pattern of the transverse colon and terminal ileum at the site of their anastomosis. Arrows indicate ulcerated involvement with irritability and spasm. Dotted line at A represents stump of terminal ileum.

tion of the transverse colon confirming roentgen-ray findings. Many minute nodules were found on the serosa of the terminal ileum which had the appearance of typical tubercles. Two enlarged lymph nodes were removed for biopsy. It was decided not to carry out any further resection of the bowel at this time, because the presence of the tubercles raised the question as to whether the underlying condition might after all be tuberculosis. The fluid in the right chest was later determined to have been caused by a small pulmonary infarct.

Following the second operation, it was decided to treat the patient as if he had tuberculosis of the intestine and peritoneum while waiting for the report of the guinea pig inoculation of the diseased glands. Accordingly, he was kept at absolute bed rest for six weeks, given daily exposures to ultraviolet ray and large doses of cod liver oil by mouth. Within a few days after commencement of this treatment, the patient's temperature became normal, his abdominal pain disappeared entirely, and although his bowel movements were still liquid, there were no abdominal cramps associated with them and the patient gained 20 pounds in weight. After four weeks of further observation in the hospital, he was discharged to a veterans' hospital near his home with the recommendation that he should be kept under observation for a period of two years and should be kept for several months on a restricted physical regime with continuation of the cod liver oil by mouth and daily exposure to ultraviolet or sunlight.

The final report of the guinea pigs inoculated with lymph node material was negative for tuberculosis. A careful reëxamination of the sections removed from the cecum, ileum and mesenteric lymph nodes also failed to reveal any evidence of tuberculosis, although many features, such as the small tubercles on the serosa of the cecum and the lymphocytic infiltration and giant cells in the submucosa were very similar to the changes seen in tuberculous processes. Several sections were sent to the Army Medical Museum for examination and the following report returned: "In our view the diagnosis of distal or regional ileitis confined to the cecum is quite acceptable in this case. The histologic picture conforms to that commonly encountered in regional ileitis. The diagnosis is further supported by the negative results from the guinea pig and negative results of other examinations for acid fast bacilli."

In reviewing the case at the time that the patient was discharged from this hospital, the question was raised as to the ultimate prognosis. In spite of a rather wide radical resection at the first operation extending 12 inches above the obviously diseased part of the ileum (confirmed by later examination of the specimen) and several inches beyond the involved portion of the transverse colon, this patient developed a local recurrence and spread of the disease from the site of anastomosis of the resected bowel within a few weeks after the resection. This indicated to us that not enough bowel had been removed. Further resection was considered at the time of the second operation but wide removal of all tissue which was suspected of being even slightly involved would have meant resecting the entire remaining colon and ileum up to the lower jejunum. The response of the patient to ultraviolet radiation, cod liver oil and the general regime of treatment usually followed in cases of tuberculous peritonitis was so satisfactory that it was felt this type of treatment should be continued.

Since discharge from this hospital in March 1944, the patient has passed out of our control and we do not know how faithfully he carried out the advice for continued ultraviolet radiation and restriction of physical activity. However, we do know that he had an acute episode of diarrhea and fever in June 1944 with abdominal pain which was treated by his physician by ultraviolet radiation and bed rest (which he apparently had not been getting previously). He showed temporary improvement on this regime but later had more fever and in August 1944 was admitted to a civilian hospital in Boston, where a diagnosis of recurrent regional enteritis was made. Roentgen-rays there showed further progression of the disease since March 1943, as evidenced by narrowing of the

lumen and mucosal changes in the remaining portion of the ileum. The patient was placed on intensive vitamin therapy and given 30,000 units of penicillin daily. After 30 days in the hospital he became afebrile and began to gain weight and have normal bowel function. He was advised to go south, probably to Florida, for prolonged rest and continued exposure to sunlight.

SUMMARY

1. A case of "regional ileitis" (granulomatous ileocolitis) involving the ileum, cecum, ascending colon, and transverse colon, is reported in a soldier 22 years old.

2. The case illustrates particularly well most of the classical features of regional ileitis including the possible etiological relationship to bacillary dysentery and the marked clinical and histologic similarity to tuberculosis. The failure to respond to usual medical treatment, such as high caloric, high protein diet, bowel sedation and sulfaguanidine medication and the tendency to recurrence even after radical surgical resection is discussed.

3. The observation was made that marked clinical improvement occurred when the patient was treated intensively with ultraviolet radiation. The effect of this treatment was temporary, however, since the patient is reported to have had symptoms of recurrent activity within six months after discharge from the hospital.

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SHORT P–R INTERVAL WITH PROLONGATION OF QRS COMPLEX AND MYOCARDIAL INFARCTION*

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THE increasing number of case reports of the Wolff-Parkinson-White syndrome has served to emphasize the need for reappraisal of the clinical aspects of this entity.

Early descriptions associated the electrocardiographic anomaly of a short P–R interval, wide aberrant QRS complex with young, healthy males not having organic heart disease. The tendency still persists to regard heart disease occur-

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ring in the presence of this syndrome as coincidental. However, the benignity of the syndrome has been challenged by one death reported by Wood et al.[1] Anatomical studies of the heart of this patient who died during an attack of paroxysmal tachycardia demonstrated an auriculoventricular accessory pathway for the aberrant conduction producing the characteristic electrocardiographic abnormalities.

Recent case histories have continued to reiterate the occurrence of the syndrome in healthy youths but paradoxically emphasize the presence of cardiac symptomatology or other stigmata of ill health of many years' duration.

Among these reports there have been noted also several episodes of paroxysmal ventricular tachycardia. It is of value to recall that in a study of ventricular paroxysmal tachycardia based on 36 studies collected from 60,000 electrocardiograms, organic heart disease was present in all but one case.[2] The most frequent precipitating factor, next to digitalis intoxication, was myocardial infarction.

Attention has been directed to the possibility of error in the diagnosis of acute coronary episode as a complication of the syndrome of auriculoventricular accessory pathway.[3, 4]

The purpose of this paper is to report a case of myocardial infarction complicating the Wolff-Parkinson-White syndrome without tachycardia.

Case Report

The patient, a white male of 33 years who had served two years and five months in the Infantry, was admitted to the Station Hospital September 19, 1944, complaining of increasingly severe precordial pain and nocturnal dyspnea of two days' duration preceded by mild sore throat, rhinorrhea and generalized malaise present since September 15, 1944. The soldier had been on extremely arduous and prolonged duty throughout the hurricane of September 14, 1944.

The family history offered no pertinent data. There was no past history of diphtheria, rheumatic fever or rheumatic equivalents; infrequent convulsive episodes occurred from infancy to age 10. Two weeks prior to present admission the soldier had been a patient in this hospital for treatment of chemical conjunctivitis. Physical examination at this time was otherwise essentially negative as were routine laboratory studies of the blood and urine. There was no history of weakness, tachycardia, palpitation, dyspnea or "wheezing cough." Throughout his military service the soldier had never reported on "sick call." His personal habits were moderate.

Physical examination on the evening of admission was entirely negative except for the presence of rhonchi and sibilant râles in all lung fields particularly at the bases. The blood pressure was 130 mm. Hg systolic and 72 mm. diastolic. The heart rate was 80. In view of the history of hurricane exposure and the lung findings the patient was admitted to the Respiratory Section.

Detailed examination by the allergist revealed no significant skin sensitivities; eye, ear, nose and throat examinations by consultant staff were reported as within normal limits.

Roentgenograms of the chest, September 23, 1944 disclosed no abnormalities of the lungs or heart.

The patient continued to complain of moderate but persistent precordial distress which became less intense since hospitalization, even while on semi-ambulatory routine. However, it was evident that the asthmatic râles were often absent throughout the day, only to appear on retiring. The patient had constantly insisted that his dyspnea and wheezes occurred at this time for which reason he disliked going to bed. Routine symptomatic therapy including subcutaneous epinephrine failed to produce

expected clinical improvement. On October 2, 1944, patient was transferred to the General Medical Section for further study.

At this time physical examination disclosed no noteworthy findings. The lungs were clear and the heart apparently normal.

Roentgen-ray examination of the heart and lungs on this date, October 2, 1944, was reported as essentially negative.

The hemogram was normal—white blood cells 10,450; polymorphonuclears 76 per cent; lymphocytes 23 per cent; eosinophiles 1 per cent. Hemoglobin 82 per cent (11.8 gm.).

The electrocardiogram showed the features of the short P–R, wide QRS abnormality. The record resembled bundle branch block of the common discordant type. The rate was 75 and regular. The P–R interval was 0.08 sec.; the QRS complex was prolonged to 0.12 sec. and the classical slurring of the ascending limb of R was present in all the limb leads. ST_2 was slightly depressed; ST_3 was isoelectric and T_3 inverted and shallow (1 mm.); RT_4 was elevated 2 mm. and T_4 was upright and large, 7 mm. (figure 1).

On the evening of October 5, 1944 the patient, who had been on ambulatory convalescent routine and apparently well except for constant unexplained precordial distress, suddenly experienced severe retrosternal pain and vertigo while sitting at his bedside and slumped to the floor in syncope. Immediately noisy rattling breath sounds were audible at a distance. The patient regained consciousness in three to five minutes, was put to bed by attendants and epinephrine administered by the nurse without, however, affecting the above lung signs. The patient was in profound shock; dyspnea was severe; the color ashen and the skin cold and moist. The heart sounds were of poor quality and muffled by the respiratory rattle. The rate was 110 mm. Hg systolic and the diastolic pressure could not be determined satisfactorily. The lungs exhibited coarse, bubbling râles which were diffusely present but most marked over the bases.

The patient responded slowly but favorably to subcutaneous morphine sulfate 0.03 gm., intravenous aminophyllin 0.3 gm. and oxygen.

The electrocardiogram taken during the acute episode showed a regular rhythm with a rate of 100. The P–R, QRS relationships were unchanged. However, RT_1 was now depressed 1 mm. and bowed down; T_1 was smaller. Depression of ST_2 was accentuated. Lead III now revealed an upright T of 2 mm. The changes in RT–T_{4f} were most marked. RT_{4-f} was now slightly depressed in marked contrast to the elevation of 2 mm. in the initial record of October 2, 1944. The T_4 waves were much smaller and suggested the M shape pattern occasionally seen in coronary insufficiency. These electrocardiographic changes were interpreted as indicating a type of acute coronary insufficiency (figure 2).

The following morning, October 6, 1944, the white blood cells numbered 17,950; polymorphonuclears 84 per cent, lymphocytes 16 per cent. Hemoglobin 88 per cent (12.7 gm.). The urinalysis was normal chemically and microscopically.

Roentgenogram of lungs and heart was essentially negative.

It was felt that this dramatic episode represented sudden left ventricular failure and cardiogenic shock precipitated by acute coronary insufficiency.

The favorable response to oxygen and supportive therapy prompted the discontinuance of digitalis, October 7, 1944, after a total of 6 cat units had been given in 36 hours in order that electrocardiographic confusion might be avoided. The temperature reached a peak of 104° the evening of October 6, 1944 but subsided to normal by October 11, 1944.

The clinical course remained uneventful thereafter except for the ever present dull precordial pain and rare asthmatic seizure, usually nocturnal.

Roentgenogram of lungs and heart, October 9, 1944, was again negative.

Blood urea nitrogen and chlorides were normal. Blood culture was negative.

Serial electrocardiograms had shown return to control tracings of October 2, 1944 by October 17, 1944.

On October 21, 1944 the patient experienced another exacerbation of precordial distress accompanied by pulmonary edema. The electrocardiogram taken during this acute episode showed regular rhythm with rate of 100. RT_1 was now depressed 2 mm.; ST_2 was depressed 1.5 mm. T_3 was diphasic to inverted (figure 3). The chest

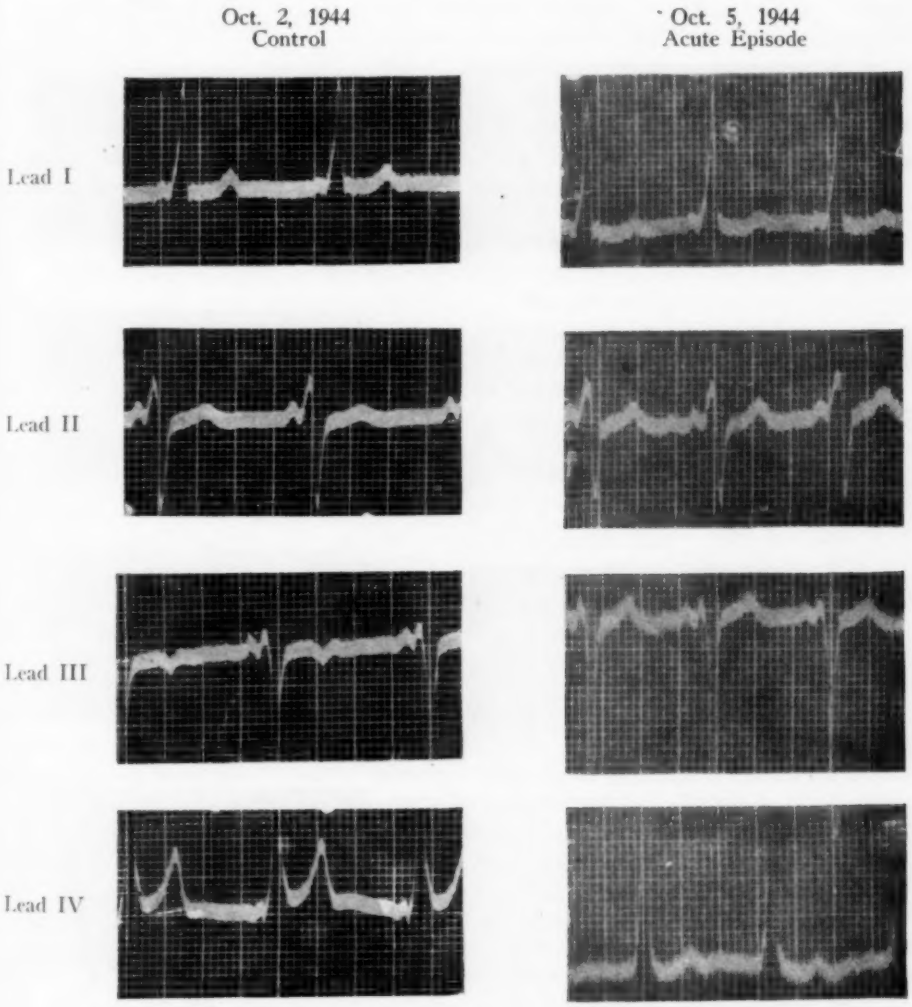

FIG. 1. FIG. 2.

lead was not obtained. Again these changes were regarded as depicting acute coronary failure.

The electrocardiogram of November 1, 1944 showed these evolutionary changes. RT_1 was slightly depressed; T_2 tiny and upright; T_3 was coved and deeply inverted, 3 mm. ST_{4-f} was again elevated to 2 mm. and T_4 had increased in amplitude to 11 mm. (figure 4).

The sedimentation rate of October 22, 1944 was reported as 24 mm. (normal 10). The white blood cell count and differential smear were normal.

Following the second acute seizure the patient developed a definite anxiety state. Hyperventilation studies with electrocardiograms and psychosomatic evaluation by the Neuro-Psychiatric Section disclosed no contradictory data.

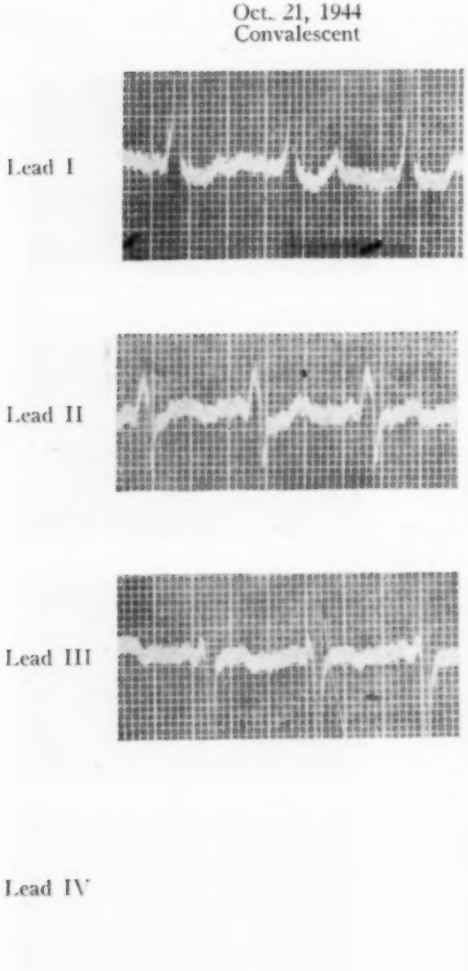

FIG. 3.

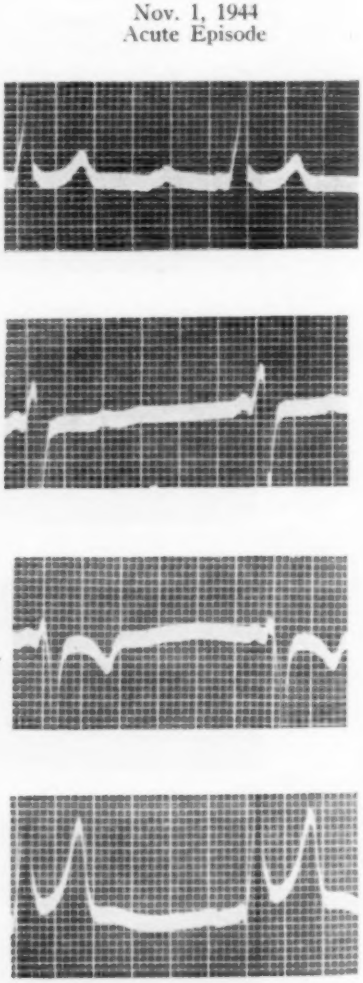

FIG. 4.

COMMENT

This case presented the electrocardiographic features characteristic of the Wolff-Parkinson-White syndrome. It differed, however, from the usual clinical entity in that paroxysmal tachycardia was never observed throughout the period of study and secondly that two acute episodes strongly suggesting coronary failure and myocardial infarction occurred.

The first attack of severe precordial pain, shock, and pulmonary edema occurring October 5, 1944 was indicative of acute coronary insufficiency or failure associated with myocardial infarction. The possibility of infarction was enhanced by the objective findings of fever, leukocytosis, and increased erythrocyte sedimentation rate. The electrocardiographic serial changes give evidence of coronary insufficiency. It is recognized that in the presence of electrocardiographic patterns of intraventricular block the coronary contour will be obscured, the resulting curve being a composite of the varying influences acting upon it.[5, 6] Appreciation of this restriction must guide the significance given to the electrocardiographic changes in this case. The spontaneous variability of contour of the T wave has been emphasized. Review of the protocols and tracings available to us indicates that the T wave variations were induced by exercise, postural changes or other procedures calculated to produce displacement or torsion of mediastinum or vagal effects and do not indicate that significant T wave changes occur when standard electrocardiographic technic is employed.

The ST–T changes in the tracings of the acute seizures of October 5, 1944 and October 21, 1944 undoubtedly comprise the pattern of coronary insufficiency. The final records demonstrate that the T waves have not returned to the measurements present in the control record of October 2, 1944 but rather, continue to suggest the coronary contour.

A recent report of Wolff-Parkinson-White syndrome simulating myocardial infarction [4] attributed the symptomatology and electrocardiographic changes entirely to the "relatively benign" syndrome. It is interesting to note that the tracings reproduced in this paper show definite evolution of the RT–T combination as usually occurs in posterior myocardial infarction. The history of this patient, clinical course, accentuated as it was by a not uncommon anxiety state, and finally serial changes in the electrocardiogram do not permit the ruling out of coronary insufficiency.

Similar misgivings are contained concerning case 4 reported by Palatucci and Knighton.[3] These authors denied the diagnosis of coronary occlusion, made by two other observers, in a patient whose history and electrocardiographic changes pointed strongly to coronary failure. Their principal objection to the diagnosis of an acute coronary episode rested on the absence of collateral findings such as increased sedimentation rate and leukocytosis. Again it is of interest to note that serial tracings never returned to the pattern of the control record.

Both of these cases exhibit insufficient consideration of anamnestic data and electrocardiographic changes which under ordinary circumstances would be of paramount aid in diagnostic and clinical appraisal.

The occurrence of coronary occlusion without myocardial infarction already has been well established.[7] French and Dock [8] have demonstrated the presence of old myocardial scars in 59 per cent of 80 fatal cases of coronary disease in soldiers aged from 20 to 36. Master has discussed the clinical pictures of coronary insufficiency and coronary occlusion. Although the diagnosis of occlusion or coronary insufficiency without infarction cannot be proved during life, inflexible insistence upon objective or collateral findings may be contrary to clinicopathologic data.

Summary

A case is reported in which a diagnosis of myocardial infarction was made on a patient having a history of severe precordial pain, shock, pulmonary edema

and an electrocardiogram characterized by short P–R interval associated with prolonged QRS.

The diagnosis is justified by occurrence at rest of sudden, severe precordial distress and collapse accompanied by electrocardiographic serial changes, fever, leukocytosis and increased erythrocyte sedimentation rate.

Despite the emphasis on the incidence of this unusual abnormality, short P–R-prolonged QRS, in apparently healthy youths, warning is restated that although the syndrome may be regarded as a rare normal variant, all such cases should be viewed suspiciously and critically.

Conservative opinion must conclude that the possibility of coronary involvement cannot be ruled out in cases having history and findings as reported herein.

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EDITORIAL

STREPTOMYCIN

"THE story of streptomycin is the story of a search for an antibiotic substance capable of exerting a bacteriostatic and bactericidal effect upon gram-negative bacteria, a substance active against these organisms not only in the test tube but also in the animal body, yet not very toxic nor exerting otherwise undesirable effects upon the body, a substance not inactivated by the body fluids and, therefore, offering chemotherapeutic potentialities." Thus runs the opening statement in the review of *Streptomycin* by Waksman and Schatz,[1] who have played such an important rôle in furnishing this new, highly potent antibiotic agent to the medical world.

It is difficult to realize that a mere ten years ago the sulfonamide drugs were added to our therapeutic armamentarium, thereby revolutionizing the chemotherapy of bacterial infections. During the next few years the clinician was confronted with a series of sulfonamide compounds, each of which was acclaimed as superior to its predecessor. And just about the time the clinician had learned the hard way of the potentialities and dangers of the sulfonamide drugs through therapeutic triumphs and therapeutic deaths, the "wonder-drug" penicillin was thrust upon his lap as a remedy more potent and less toxic than the sulfonamide compounds. Now that penicillin is readily available—although still expensive—it is distressing to observe the indiscriminate use of this drug in practically every patient who develops an elevation of temperature.

Granting that the sulfonamides and penicillin are highly potent therapeutic agents against many bacterial infections, it is generally accepted that their chief value lies in the treatment of infections due to gram-positive organisms such as the streptococcus, staphylococcus, and pneumococcus. To be sure, both the sulfonamides and penicillin have proved highly effective against certain gram-negative cocci such as the meningococcus and gonococcus, while certain sulfonamides have served to suppress such gram-negative bacillary infections as acute brucellosis, colon bacillus urinary tract infections, and infections due to *Hemophilus influenzae*. However, there are many infections due to gram-negative organisms in which both the sulfonamides and penicillin proved to be relatively ineffective. It is for the treatment of such infections that streptomycin offers the greatest promise.

In 1939 Waksman and his associates in the Department of Microbiology of the New Jersey Agricultural Experiment Station at Rutgers University began to study production of antibiotic substances by microörganisms. Some thousands of actinomycetes, hundreds of fungi and many bacteria were isolated from normal soils and enriched soils, from composts, manures and

[1] WAKSMAN, S. A., and SCHATZ, A.: A review . . . streptomycin, Jr. Am. Pharmaceut. Assoc., Practical Pharmacy Edition, 1945, vi, 308.

peat bogs as well as from other natural materials. Special methods were devised for the isolation of antagonistic organisms and technics were developed for the production, isolation, and study of the active antibacterial substances. The isolation of streptomycin must, therefore, be regarded as the result of extensive surveys, detailed analyses and numerous tests in which many collaborators have participated. These studies resulted in the isolation of an actinomyces which was found capable of producing, in certain media, an antibiotic substance that apparently possessed many of the desirable antibacterial and pharmacologic properties. This substance was designated as streptomycin, the name being derived from the generic designation given to the sporulating and aerial mycelium-producing group of actinomycetes, *Streptomyces*. Characteristics of these organisms relate them to both bacteria and molds.

Crystalline streptomycin is now available which, in contrast to penicillin, is markedly stable both chemically and biologically. The pure base possesses an activity of about one unit per microgram. The action of streptomycin is generally bacteriostatic in low concentrations and bactericidal in higher concentrations. It is active in vitro against a variety of pathogenic gram-positive and gram-negative bacteria, including *Mycobacterium tuberculosis, Eberthella typhosa, Pasteurella tularensis, Klebsiella pneumoniae* (Friedländer's bacillus), *Brucella abortus, Proteus vulgaris, Hemophilus pertussis, H. influenzae, Pseudomonas aeruginosa*, and many others.

Studies on the absorption and excretion of streptomycin in animals have shown that this antibiotic, administered parenterally, behaves like penicillin in that both agents are rapidly absorbed and rapidly excreted in the urine. Therapeutic blood levels are easily produced by intravenous or subcutaneous injections. Oral dosage, on the other hand, results in very low blood concentrations. The toxicity of streptomycin, especially of purified preparations, was found to be extremely low. When present, it revealed itself in animals usually as a histamine-like reaction. A second toxic effect, namely fatty infiltration of the liver and occasionally of the kidneys, was especially pronounced in monkeys following prolonged administration of large doses of streptomycin. The latter type of reaction has never been observed in man even after prolonged administration of as much as 4.0 grams of streptomycin daily. Streptomycin has been administered to human beings intramuscularly, intravenously, and subcutaneously, both by intermittent injection and by continuous drip. It has also been given intrathecally, orally, and by nebulization into the tracheobronchial tree. When ingested, streptomycin is not appreciably absorbed nor is it destroyed in the intestine. This persistence and stability in the gut has been used to advantage for the treatment of typhoid patients. After parenteral administration, streptomycin has been detected in ascitic and pleural fluids in concentrations approximating the level in the blood, whereas diffusion from the blood stream into the cerebrospinal fluid is generally slight.

To date streptomycin has been administered [2] with highly encouraging results to patients with heretofore resistant gram-negative bacillary infections of the urinary tract, typhoid fever, tularemia, pulmonary and meningeal infections due to Friedländer's bacillus and *Hemophilus influenzae*, bacteremias due to gram-negative bacilli such as *Proteus vulgaris, Escherichia coli, Aerobacter aerogenes* and *Salmonella*, and wound infections. Furthermore there is suggestive evidence that streptomycin may prove beneficial in the treatment of acute brucellosis and tuberculosis although no definite conclusion may be drawn as yet. Although exerting some suppressive action against *Treponema pallidum, Borrelia novyi,* and *Leptospira icterohaemorrhagiae,* streptomycin has proved to be far less effective than penicillin in the treatment of syphilis and other spirochetal infections. Streptomycin has also proved valuable in the treatment of infections due to the gram-positive *Streptococcus faecalis* which is unaffected by sulfonamides or penicillin.

Streptomycin has a limited but definite toxicity [3] for human beings. The most serious reaction is a vestibular disturbance, causing dizziness, tinnitus, ataxia, and occasionally transient deafness. This reaction has occurred after large doses have been administered over long periods; it has not been observed in cases in which only short courses of treatment (up to two weeks) have been employed. This reaction warrants interruption of drug therapy. Irritation and pain at the site of injection are common; for this reason rotating the sites of intramuscular injections is recommended. Toxic erythema and a diffuse generalized morbilliform cutaneous rash with fever and eosinophilia may occur at times after several days' administration of streptomycin. Arthralgias, myalgias, headache, nausea and vomiting, probably due to impurities, have been observed after the administration of certain batches of streptomycin. Some renal irritation, manifested by a transient increase in urinary output, hematuria, and cylindruria, has been noted following the administration of large doses.

The supply of streptomycin is limited as yet, and total allocation of the drug is now in the hands of the Civil Production Administration. It is now being allocated to the Army, Navy, Veteran's Administration, U. S. Public Health Service, and the Committee on Chemotherapeutic and Other Agents of the Division of Medical Sciences of the National Research Council. No one other than the agencies named may purchase streptomycin. No patient who receives it may pay for it; no physician is charged for it. Streptomycin for civilian use is placed in charge of the chairman of the committee of the National Research Council for distribution to those hospital physicians most competent to obtain the vitally needed information regarding the diseases which are to be investigated under this committee. The chairman, Dr. Chester Keefer,[4] has recently published an official statement listing those dis-

[2] HERRELL, W. E., and NICHOLS, D. R.: The clinical use of streptomycin: a study of forty-five cases, Proc. Staff Meet. Mayo Clin., 1945, xx, 449.

[3] Streptomycin. A review of current experience, Bull. U. S. Army Med. Dept., 1946, v, 531.

[4] KEEFER, C. S.: Official statement concerning streptomycin, Jr. Am. Med. Assoc., 1946, cxxxi, 31.

eases which are at present under investigation. Any physician desiring streptomycin would do well to consult this list before requesting the drug in order to determine whether his patient is "eligible."

Streptomycin, then, is here to stay, at least until some superior antibiotic preparation comes along to supersede it. And if such a super-drug is developed, it too will in all likelihood emerge from the earth under our feet. To one with a philosophical twist, it must seem mildly entertaining to reminisce over the major advances in antibiosis during the past twenty years. Starting with the pneumococcal polysaccharide-splitting enzyme culled from a cranberry bog, we have seen gramicidin, tyrothricin, penicillin, streptothricin, and finally streptomycin "sprout" from the soil in rapid succession. At the rate things are going the bacteriologists and chemotherapists may soon supplant the sociologists as the prime supporters of the "back-to-the-soil" movement!

W. H. B.

CORRESPONDENCE

Treatment of Rheumatic Heart Disease by Roentgen-Ray Irradiation

July 8, 1946

To the Editor:

In the Annals of Internal Medicine for June, 1946 (p. 1039), there was published an article by Griffith and Halley entitled "The Treatment of Rheumatic Fever by Roentgen-Ray Irradiation." These authors referred to a series of four papers published by us between 1926 and 1933, and reached conclusions apparently at variance with ours. Our last paper, "Roentgen Therapy of Active Rheumatic Heart Disease: A Summary of Eleven Years' Experience" (Am. Jr. Med. Sci., 1937, cxciv, 597), was not cited.

A comparison of material and method readily serves to indicate the reasons for the discrepancies. They evidently were concerned with the general manifestations of rheumatic fever rather than primarily with its cardiac aspects. Their cases were classified as acute fulminating, subacute polycyclic, subacute monocyclic and subclinical. No description was given of the cardiac status of their patients. Our attention was focused on the heart.

They did not follow the technic of irradiation which we recommended. In our studies, approximately 60 r, as measured in air without back-scattering, was applied to the front of the chest, and from 100 to 125 r to the back, depending upon the depth of the patient's thorax. The object was to distribute approximately 60 r, as measured in air, throughout the heart area. The treatments were given at intervals of two weeks for four sittings. Then a period of one to three months was allowed to elapse and the series was repeated. The number of treatments given to an individual ranged from 3 to 25, with an average of 9. Twelve cases received 10 or more. In general, those receiving the larger number of treatments fared best.

To one group of patients, Griffith and Halley gave "100 r through the myocardium"; another group received the same dose through the myocardium and also over the middle and lower cervical sympathetic ganglia. This statement does not make it clear whether 100 r was the measurement in air or whether it represented an estimate of tissue dose. The treatments were given at weekly intervals for five successive weeks.

In the light of our experience, we feel justified in repeating some of our conclusions stated in 1937: (1) In a considerable number of patients irradiation therapy exerted a favorable effect upon the lesions in the heart and upon the course of the disease; (2) irradiation relieved cardiac pain in patients who did not have aortic insufficiency; (3) no harmful effects were noted; (4) cases with low-grade activity and without signs of congestive heart failure appeared to be most benefited whereas the acute cases were not improved; (5) roentgen irradiation of the heart, in the present state of knowledge concerning rheumatic fever, deserves a place as a therapeutic measure in properly selected cases of active carditis.

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Ross Golden, M.D.
Presbyterian Hospital
New York City.

REVIEWS

Diseases of the Adrenals. By Louis J. Soffer, M.D. 304 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia, Pa. 1946. Price, $5.50.

The author states in his preface that he has attempted to present the present day knowledge of both the physiology and diseases of the adrenals. He has fulfilled his purpose in all respects. After a brief description of the anatomy of the glands, the laboratory technics of value in the diagnostic survey of a suspected case of adrenal dysfunction are outlined. An interesting discussion of the physiology of the adrenal glands, with emphasis on their endocrine inter-relation, facilitates the detailed discussion of Addison's disease and the Waterhouse-Friderichsen syndrome which follows. The management of an Addisonian crisis is well presented and the author properly emphasizes the dangers of over-zealous pellet implantation in the treatment of Addison's disease.

The morbid states associated with adrenal cortical hyperfunction are grouped under the title "Adreno-genital Syndrome." This may prove misleading for those who reserve the term for the condition characterized predominantly by disturbances in sexual physiology; however, our understanding of the basic aberrations in adrenal cortical hyperfunction is still incomplete and new approaches to the problem are warranted. Perhaps the use of Talbot's method of assaying 11-Oxycorticosteroids, used more widely, will lead to a clarification.

The bibliographies at the end of each chapter are excellent, and, whenever possible, discussions of diagnoses or therapy are effectively summarized at their conclusion.

This book will prove invaluable to any physician dealing with adrenal disorders.

J. Z. B.

Human Gastric Function. An Experimental Study of a Man and His Stomach. By Stewart Wolf, M.D., and Harold G. Wolff, M.D.; Foreword by Walter B. Cannon. 195 pages; 16 × 24 cm. Oxford University Press. 1943. Price, $4.75.

This study of a man and his stomach should be read by every physician, practitioner, specialist and research man. It should be read by those who reject or are skeptical about the "psychosomatic approach," as well as by those who are sold on it but too often do not take the trouble to study carefully both aspects, the somatic and the psychological, and to correlate the two series of findings.

The subject of this study, a 57 year old man, presented an unusual opportunity for the investigation of the behavior of a human stomach. Tom, at the age of 9, had been operated on for an esophageal stricture resulting from drinking extremely hot clam chowder. The lumen of the esophagus could not be kept open and a gastrostomy had to be performed. "The anterior portion of the greater curvature of the stomach was brought out and sutured to the abdominal wall," but a plastic closure could not be done. Tom was "left with a defect in his abdominal wall 3.5 cm. in diameter, through which a collar of redundant gastric mucosa herniated. Thereafter, he fed himself through the artificial opening," first chewing the food in his mouth and then spitting it into a funnel with attached rubber hose that he inserted into his stomach.

The authors thus had the opportunity for prolonged close inspection of the stomach mucosa, that is of the exposed collar of the mucous membrane as well as of the interior of the stomach (by inserting a lighted anoscope).

Various functions of the stomach, as well as the behavior of the stomach mucosa under different conditions, were studied over a period of months. Tom was made attendant in the laboratory where the project was carried out. This not only had the

advantage of his being available at any time, it also afforded the opportunity of studying the man in an environment which, after a while, lost its artificiality for him and became his natural habitat.

A careful study of Tom's background and personality is presented. The behavior of the stomach, changes in blood flow, motor activity and secretion, were studied under varying conditions and influences, especially under the influence of common physical and chemical agents, and under that of various life situations and accompanying emotional states. The effect on the stomach mucosa of temperature changes, mechanical irritation, tobacco smoking, acids and antacids, various drugs ranging from nitroglycerin and atropin to pitressin and acetylcholine, was investigated. One of the important findings here was the observation that the effect of one and the same drug on the gastric mucosa varied according to the emotional condition of the subject at the time of the experiment.

"Emotionally charged situations were not experimentally induced but spontaneously occurring life problems and conflicts were utilized. . . . His reaction to each of these experiences was evaluated in the light of his personality pattern. . . . Thirty-four observations of stomach function accompanying several different affective states were made." Illustrative examples are presented.

The importance of this experimental study for the understanding of "gastritis" and ulcer formation can be deduced from the following conclusions: "Undue and prolonged acceleration of acid secretion in the stomach, however provoked, resulted in hyperemia and engorgement of the mucous membrane resembling hypertrophic gastritis. The mucosa in this state was unusually susceptible to injury, and even the most trifling traumata resulted in hemorrhages and small erosions. Ordinarily the mucosa was protected from injury by an effective coating of mucus. Loss of this protection in the face of minor traumata led to oedema, inflammatory changes, erosions, and hemorrhages. Contact of acid gastric juice with a denuded surface induced further hyperemia and acceleration of acid secretion. Prolonged contact of acid juice with a minor erosion resulted in the formation of a peptic ulcer." It is interesting to note that the ulcer thus produced in the subject over a period of four days, disappeared completely, leaving no trace of a lesion, within three days during which the area was covered with a protective petrolatum dressing.

Alterations in gastric function, paralleling emotional disturbances, fell into two categories: (1) depression of acid output, motor activity and vascularity, "associated with a reaction of flight or withdrawal from an emotionally charged situation;" (2) acceleration of these functions, associated with "a reaction of internal conflict, with an unfulfilled desire for aggression and fighting back." "Profound and prolonged emotional disturbances of this kind were accompanied by marked and prolonged increases in gastric motility, secretion, and vascularity, with reddening and engorgement of the mucous membrane, often reproducing the picture of 'gastritis'." Vasomotor changes observed in the stomach often corresponded to similar pallor or blushing of the face. There was also a correlation between the amount of activity of the stomach on one hand and the amount of talkativeness and general body activity on the other hand. "The altered gastric function," the authors conclude, "was merely a part of the whole pattern of bodily reaction," in the face of mechanical and pharmacological stimulation as well as under the influence of situational and emotional factors.

In the light of their findings, suggestions as to the clinical management of gastritis and ulcer patients are offered, which should be helpful to general practitioners, surgeons, psychiatrists and internists alike.

Diagrams and other illustrations are clear, simple and truly illustrative. The book is a remarkable example of a complex research project concisely and lucidly presented.

H. W. L.

Men under Stress. By Lt. Colonel Roy R. Grinker, M. C., and Major John P. Spiegel, M.C., Army Air Forces. 484 pages; 16 × 24 cm. Blakiston Co., Philadelphia. 1945. Price, $5.00.

This is one of the most important publications in the field of military psychiatry to appear on the market during the second World War. It is written by two psychiatrists who were connected with the Army Air Forces overseas and later with Don Cesar Hospital, an Army Air Force convalescent hospital receiving cases of war neuroses. They therefore had a chance to study reactions before and after combat and actually to follow up some men whom they had sent home. This book is the second one of the authors; their first was a study of psychologically wounded Ground Force soldiers and appeared earlier as a "restricted" military monograph. Two books make for interesting comparisons, and their differences add more to the field of psychiatric research.

The present work is clearly and interestingly written with a wealth of case material and discussion. Points of theory are carefully developed and conclusions are drawn which are sound and applicable to practical use. The authors build up their work in almost a novel form. Their thesis is that "under sufficient stress any individual may show failure of adaptation, evidenced by neurotic symptoms." War tries men as a cruel experiment and hard though it may be, "valuable lessons" can be learned about man's adaptation and applied to problems of civilian living. The authors add that the problems of the peace following the war may put as much strain on man as those of the war. With the thesis thus stated, they develop the plot by first describing the men of the Army Air Forces, their motivations, conscious and unconscious, to become fliers, and their selection physically, psychologically and psychiatrically by the army. Important conclusions as to who were capable psychiatrically of flying were obtained mostly after the test of combat. Some individuals deemed good material for combat flying developed "operational fatigue," whereas others suffering from neurosis in civilian life were able to endure a complete tour of combat duty. The next section of the book is devoted to what the environment of combat is like—how A.A.F. units are formed, their motivation to fight and how dependent morale is on the composition of the unit—each individual contributing personally to the morale of the whole and of each member. The third and fourth sections deal with the reactions to combat stress and to the return home. These sections comprise the bulk of the book and are concerned with quoting of case material, psychodynamics, and treatment. The authors make a distinction between reactions to combat based on previous neuroses and neurotic reactions of "stable" individuals to severe stress. They cannot come to definite conclusions regarding differential prognoses of the second class because of their inability to follow up enough cases. The final section is concerned with civilian applications—the importance of psychiatric understanding in general medical practice and the great need for many more properly trained psychiatrists, also the addition of new treatment procedures and further proof of some theories existing before the war and now having the benefit of mass validation. A final note of warning is issued by the authors for the treatment of the returned soldier—unless we have a program that meets his psychological needs, we stand in grave danger of political upheavals, pension armies, and other forms of sociological behavior which arise from psychological maladjustment.

This book should have a wide appeal to the psychiatrist, the general practitioner and the intelligent layman. It is theoretically sound, based on modern dynamic psychology, yet not too theoretical for those outside the field. The style is clear and has literary merit. There is some annotation but not enough to make the book ponderous or obviously scholarly. The bibliography is good, although not long.

H. W. N.

What People Are. A Study of Normal Young Men. By CLARK W. HEATH, Dept. of Hygiene, Harvard University. 141 pages; 21.5 × 14.5 cm. 1945. Harvard University Press, Cambridge, Mass. Price, $2.00.

This little book, as stated in the preface, is a "brief introduction to the point of view of the Grant Study and the methods used in the effort to study normal human beings." It is divided into three sections, the first an explanation of the selection of subjects, the general plan of study and the methods used in examining the subjects. The subjects used were Harvard students, in their second year of college work. They were chosen for their satisfactory records both academically and in their relationship with others. They had no physical or psychological abnormalities of sufficient magnitude to warrant reporting on the college records. These boys were studied by a group consisting of a physician trained in internal medicine, a physiologist, a physical anthropologist, a psychologist, two psychiatrists and a personnel worker in charge of collecting socio-economic information.

The second and main portion of the book goes into considerable detail describing the findings of this study. According to their findings, the author has divided their subjects into three fairly well differentiated types of normal personalities and has pointed out their outstanding traits. They have found relationship between body build and personality features. Many interesting things, suggestive of correlation in other fields were brought out, but further study and follow up will be necessary before any definite statements can be made.

The third part of the book points out that further study of this group and of other groups of young men with a view to comparing them with this selected group of young men, is desirable. It also sums up the follow-up work which has been done and which is to be continued throughout the lifetime of the participants.

The book is interesting and informative. Anyone interested in people, normal or abnormal, will find in it much of importance, together with suggestions of a new approach to finding out "what people are." It is admittedly an introduction, but one which will stimulate all who read it and cause them to await with interest further publications on the Grant Study.

R. K. G.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Principles of Bacteriology and Immunity. W. W. E. TOPLEY, and G. S. WILSON. Two volumes. Vol. I, 970 pages; 24.5 × 17 cm. Vol. II, 2054 pages; 24.5 × 17 cm. 1946. Williams & Wilkins, Baltimore. Price, $12.00.

A Textbook of the Practice of Medicine. By various authors. Edited by FREDERICK W. PRICE, M.D. Seventh Edition. 2034 pages; 23 × 14.5 cm. 1946. Oxford University Press, New York. Price, $13.50.

Through the Stratosphere. The Human Factor in Aviation. By MAXINE DAVIS. 253 pages; 22 × 14.5 cm. 1946. The MacMillan Company, New York. Price, $2.75.

The Early Diagnosis of the Acute Abdomen. By ZACHARY COPE, B.A., M.D., M.S. 262 pages; 22.5 × 14.5 cm. 1946. Oxford University Press, New York. Price, $3.75.

A Manual of Tuberculosis. By E. Ashworth Underwood, M.B., B.Sc., M.D. Third Edition. 524 pages; 19.5 × 13 cm. 1945. The Williams & Wilkins Company, Baltimore. Price, $4.50.

Neurosis and the Mental Health Services. By C. P. Blacker, M.A., M.D., F.R.C.P. 219 pages; 22 × 14.5 cm. 1946. Oxford University Press, New York. Price, $5.00.

A B C of Medical Treatment. By E. Noble Chamberlain, M.D., M.Sc., F.R.C.P. 206 pages; 19 × 12.5 cm. 1946. Oxford University Press, New York. Price, $3.00.

Studies in Hypertony and the Prevention of Disease. By I. Harris, M.D. 114 pages; 19 × 12.5 cm. 1946. The Williams & Wilkins Co., Baltimore. Price, $3.00.

Autopsy Diagnosis and Technic. By Otto Saphir. Second Edition, revised. 405 pages; 19.5 ×13.5 cm. 1946. Paul B. Hoeber, Inc., New York. Price, $5.00.

Medical Jurisprudence and Toxicology. By John Glaister. Eighth Edition. 691 pages; 22 × 14.5 cm. 1945. Williams & Wilkins Company, Baltimore. Price, $8.00.

Psychological Medicine. Second Edition. By Desmond Curran, M.B., F.R.C.P., and Eric Guttman, M.D., M.R.C.P. 246 pages; 22 × 14.5 cm. 1945. The Williams & Wilkins Company, Baltimore. Price, $3.50.

Narcotics and Drug Addiction. By Erich Hesse, M.D.; translated by Frank Gaynor. 219 pages; 24 × 15.5 cm. 1946. The Philosophical Library, Inc., New York. Price, $3.75.

Renal Diseases. By E. T. Bell, M.D. 434 pages; 23 × 15.5 cm. 1946. Lea & Febiger, Inc., Philadelphia. Price, $7.00.

The Modern Treatment of Diabetes Mellitus. By William S. Collens, B.S., M.D., and Louis C. Boas, A.B., M.D. 514 pages; 23 × 15.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, $8.50.

Manson's Tropical Diseases. Twelfth Edition. Edited by Philip H. Manson-Bahr. 1068 pages; 22.5 × 15 cm. 1945. Williams and Wilkins Company, Baltimore. Price, $12.00.

Diseases of the Retina. By Herman Elwyn, M.D. 587 pages; 23.5 × 16 cm. 1946. The Blakiston Company, Philadelphia. Price, $10.00.

COLLEGE NEWS NOTES

A.C.P. Regional Meeting, Pittsburgh, Sept. 25

Under the Governorship of Dr. Roy R. Snowden, Pittsburgh, a Regional Meeting of the College for Western Pennsylvania will be held at the Medical Center, Wednesday, September 11, 1946.

This meeting comes in the midst of an A.C.P. Postgraduate Course in Internal Medicine under the direction of Dr. Snowden at the University of Pittsburgh, September 2–14. The Regional Meeting program also becomes a part of the course for that day. The theme of the scientific program for the Regional Meeting will be "Frontiers of Science." Dr. W. S. McEllroy, F.A.C.P., Dean of the University of Pittsburgh School of Medicine, will preside. There will be a description and demonstration of the ultra-centrifuge, electron microscope and cyclotron.

The latest knowledge of the atom and molecule, and the applicability of this knowledge in medical science will be presented by Max A. Lauffer, Ph.D., Associate Research Director, Department of Physiological Chemistry, University of Pittsburgh, and Alexander J. Allen, Ph.D., Westinghouse Graduate Professor of Engineering, University of Pittsburgh. The Annual Regional Banquet will be held, followed by short addresses by distinguished guests. Those enrolled in the course as well as all instructors will be guests of the College.

Forthcoming Board Examinations

The next examination of the American Board of Psychiatry and Neurology will occur in December 1946 in New York. More specific information as to date and location will be given in a later issue of the Annals.

The 1946 examinations of the American Board of Radiology will be given in Chicago at the Palmer House, November 27–30, 1946.

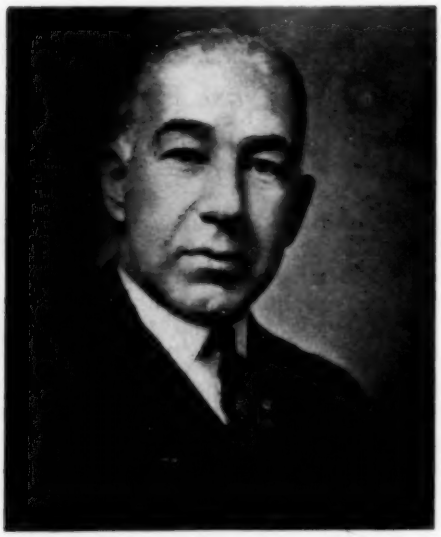
The College has been advised that the oral examination of the American Board of Internal Medicine will be given in Chicago, October 29, 30 and 31, 1946. Candidates will note the addition of October 29 to the dates previously announced.

Gifts to the College Library

The following gifts of publications by members are gratefully acknowledged:

D. E. H. Cleveland, F.A.C.P., Vancouver, B. C., Can.—1 reprint.
Samuel Cohen, F.A.C.P., Jersey City, N. J.—2 reprints.
Samuel E. Cohen (Associate), Elmira, N. Y.—4 reprints.
Charles A. R. Connor (Associate), New York, N. Y.—1 reprint.
Lewis J. Moorman, F.A.C.P., Oklahoma City, Okla.—3 reprints.
Frederick W. Mulsow, F.A.C.P., Cedar Rapids, Iowa—2 reprints.
Sidney L. Penner (Associate), Fort Bragg, N. C.—2 reprints.
George X. Schwemlein (Associate), Cincinnati, Ohio—2 reprints.
Ramon M. Suarez, F.A.C.P., Santurce, San Juan, P. R.—2 reprints.

At the recent meeting of the American Medical Association in San Francisco, Dr. Edward L. Bortz, F.A.C.P., Philadelphia, College Governor for Eastern Pennsylvania, was elected vice-president. Dr. Olin West, who recently retired as General Secretary of the American Medical Association, was elected President-elect. Dr. Francis F. Borzell, F.A.C.P., Philadelphia, was reëlected Speaker of the House of Delegates.



Dr. Edwin Joseph Cohn, 1946 Phillips Medalist, The American College of Physicians

Dr. Edwin Joseph Cohn Receives the John Phillips Memorial Medal from the American College of Physicians

The American College of Physicians awards periodically the John Phillips Memorial Medal to a scientist of the United States or Canada, who is recognized by the Board of Regents, upon recommendation of the Committee on Fellowships and Awards, as having made the most significant contribution to research in the field of internal medicine for the immediate preceding period.

Dr. Edwin Joseph Cohn, Professor of Biological Chemistry and Head of the Department of Physical Chemistry of Harvard Medical School, and Chairman of the Division of Medical Sciences of the Faculty of Arts and Sciences, Harvard University, Boston, was chosen for the 1946 award. His citation reads as follows:

"Eminent scientific investigator, whose distinguished research on the physical chemistry of amino acids, peptides, and proteins has brilliantly elucidated the chemical interactions of biological systems and made possible the separation of the components of concentrated solutions rich in proteins, for exceptionally meritorious accomplishment in the fractionation of human plasma into purified substances of preventative and therapeutic value. Through exacting and meticulous research, fraught with the romance of new and incredibly intricate techniques of isolation, measurement and definition, in the realm of ultracentrifuges and ingenious optical systems, of streaming birefringence, diffusion constants and viscosity coefficients, of electrical charge distributions, atomic relations and ionic atmospheres, Dr. Cohn has devised and directed the partition of human plasma by physical-chemical methods and the preparation, primarily for use of the armed forces on the battle fields of the world, of at least five products possessing important clinical uses: albumin for combatting shock, isohemagglutinins for blood grouping, fibrinogen and thrombin for hemostasis, and gamma globulin for passive immunization against epidemic disease. The field of usefulness of all these new products is only beginning to be explored and is limited only by the ingenuity of chemists to devise new forms and the imagination of physicians and surgeons to employ them. Above all stands the felicitous fact that these substances are derived from native human proteins and all the errors and problems of foreign body reactions are at once resolved."

Appointment Sought in the Field of Pathology

A Fellow of the American College of Physicians who has had a distinguished career in the Medical Corps of the U. S. Army, now 62 years of age, seeks an appointment commensurate with his knowledge of pathology and experience. His credentials are: A.B. and M.D., Columbia University; postgraduate study at the Army Medical School and in Vienna, Austria, under Chiari and Erdheim; three years internship, New York Hospital; diplomate, American Board of Pathology; 36 years of active duty in the U. S. Army, including surgery, obstetrics, x-ray clinical laboratory procedures including bacteriology and serology, and during the past 20 years, gross and micropathology; teaching and lecturing; during World War I, in charge of Army Laboratory No. 1 in France; now in charge of a Service Command Laboratory, where duties include those of Chief of Pathological Section; member of numerous national medical societies, including the American College of Physicians; author of numerous publications in leading medical journals.

The Executive Secretary, Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Pa., may be consulted concerning other qualifications of the candidate.

Internist Wanted

A Fellow of the American College of Physicians, located in California, is desirous of obtaining an internist for association with him in practice. A doctor, under the age of forty, certified by the American Board of Internal Medicine, or eligible for certification, who would be interested in a connection first on a salary basis and later, if mutually agreeable, to form a partnership, is desired. Any interested physician should communicate with the Executive Secretary of the College, Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Pa.

Correction

In the June, 1946, issue of this journal, it was announced that Dr. William L. Howell, F.A.C.P., had retired from the Medical Corps, A.U.S., with rank of Major.

Dr. Howell was promoted to the rank of Lieutenant Colonel on June 1, 1945, and was recently (April 29, 1946) placed on inactive status. He is now engaged in the practice of internal medicine at 1801 Eye St., Northwest, Washington, D. C.

University of California Offers Refresher Course

The University of California Extension Division and the Department of Psychiatry of the University's Medical School have announced a twelve weeks refresher course in psychiatry and neurology, which is to be given, under the direction of Dr. K. M. Bowman, Professor of Psychiatry, at the Langley Porter Clinic, San Francisco. Registration is limited to 60 doctors; preference will be first to graduates of the Medical School and to veteran physicians. Among the subjects to be covered are psychobiology, psychoses and psychoneuroses, clinical neurology, and electroencephalography. The fee for the course is $200, payable in advance. Dr. Stacy R. Mettier, F.A.C.P., Head of Postgraduate Instruction, Medical Center, University of California, San Francisco 22, Calif., will receive applications for registration.

Dr. R. Manning Clarke, F.A.C.P., removed from Camden, N. J., toward the end of June to San Diego, Calif., where he has become the internist for the Sand-Oster Clinic.

Dr. Horace K. Richardson, F.A.C.P., Baltimore, was recently elected President of the Maryland Association of Private Practicing Psychiatrists.

Associate Internist Wanted

A Fellow of the American College of Physicians, located in Indiana, is desirous of obtaining an associate in the practice of Internal Medicine. He is a man widely known with a large practice. He wants an associate who is already certified by the American Board of Internal Medicine, or one who, at least, has the necessary background for certification; an extraordinarily good opportunity for some internist who is anxious to establish himself and who is willing to carry his part of the load. Any interested physician should communicate with the Executive Secretary of the College, Mr. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa., making reference to "AO–2."

The War Department has announced the appointment of consultants in neuropsychiatry to the Secretary of War. The first consultant is to be Dr. William C. Menninger, F.A.C.P., Topeka, Kan.; other members of the College appointed as consultants are Dr. Lauren H. Smith, F.A.C.P., St. Louis, Mo.; Dr. Norman G. Brill (Associate), Silver Springs, Md.; Dr. John H. Greist (Associate), Indianapolis, Ind.; Drs. Clarke H. Barnacle, F.A.C.P., Edward G. Billings, F.A.C.P., and Franklin Ebaugh, F.A.C.P., all of Denver, Colo.

Brigadier General W. Lee Hart, U. S. A. (retired), F.A.C.P., has been honored by the award of the degree of Doctor of Humanistic Letters by the Southwestern Medical Foundation of Dallas, Tex.

Dr. Walter L. Bierring, F.A.C.P., Des Moines, has been appointed Professor Emeritus of Theory and Practice of Medicine in the State University of Iowa College of Medicine.

Dr. Albert D. Foster, F.A.C.P., Portland, Me., has been appointed health officer of that city.

Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, has received appointment as consultant to the Veterans Administration.

Dr. E. Sterling Nichol, F.A.C.P., Miami, Fla., has been elected president of the Florida chapter of the American College of Physicians.

Dr. Julius L. Wilson, F.A.C.P., and Dr. Maurice Campagna, F.A.C.P., New Orleans, were recently reëlected President and Vice-President, respectively, of the Louisiana Tuberculosis Association.

On the occasion of the recent annual meeting of the Medical Society of the State of North Carolina, Dr. George E. Bell, F.A.C.P., Wilson, was elected First Vice-

President of the Society. Dr. James Bullitt, F.A.C.P., Chapel Hill, was elected Second Vice-President. Drs. W. C. Davison, F.A.C.P., Durham, and C. C. Carpenter, F.A.C.P., Winston-Salem, were elected to the Editorial Board of the North Carolina Medical Journal.

Dr. Dunne W. Kirby, F.A.C.P., formerly on the faculty of the Hahnemann Medical College and Hospital of Philadelphia, who served through the war in the Medical Corps of the Naval Reserve, has transferred to the Regular Navy with the rank of Commander, and is now stationed at the U. S. Naval Hospital, Newport, R. I.

Dr. Henry P. Close (Associate), Philadelphia, has retired from private practice and is now devoting his whole time to the Veterans Administration as Chief of the Medical Service, Coatesville Veterans Hospital, Coatesville, Pa.

The Kansas City Southwest Clinical Society will hold its 24th Annual Fall Clinical Conference, October 7–19, 1946. According to advanced announcements, the following members of the College will be guest speakers:

Charles A. Doan, M.D., F.A.C.P. (Internal Medicine, Research), Columbus, Ohio;

Tinsley R. Harrison, M.D., F.A.C.P. (Internal Medicine, Cardiology), Dallas, Tex.;

Walter L. Palmer, M.D., F.A.C.P. (Internal Medicine, Gastro-enterology), Chicago, Ill.

Dr. George W. Millett, F.A.C.P., formerly of San Francisco, has become Senior Medical Officer, Veterans Hospital, Montgomery, Ala.

Dr. Charles H. McEnerney, F.A.C.P., Washington, D. C., has been elected Third Vice-President of the Pan American Medical Association.

Dr. Felix J. Underwood, F.A.C.P., Jackson, Miss., executive officer of the Board of Health of the State of Mississippi, was a speaker at the dedication ceremonies of the North Mississippi Hospital.

Dr. Millard E. Winchester, F.A.C.P., Brunswick, Ga., has been elected President-elect of the Georgia Public Health Association.

Dr. Laurrie D. Sargent, F.A.C.P., presided at the Annual Meeting of the Tenth and Eleventh Councilor Districts of the Medical Society of the State of Pennsylvania, held at Washington, Pa., June 20. Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, presented 50-year testimonials to 15 members of the Society. Scientific papers were presented by Dr. Howard K. Petry, F.A.C.P., Harrisburg, and Dr. George J. Kastlin, F.A.C.P., Pittsburgh, Pa.

The Forty-Seventh Annual Meeting of the American Gastroenterological Association occurred May 24–25 at Atlantic City. Dr. A. H. Aaron, F.A.C.P., Buffalo, N. Y., delivered the presidential address and presented the Friedenwald Medal of 1946

to Dr. Frank H. Lahey and Dr. Sara Jordan, F.A.C.P., Boston. The following Fellows of the College presented papers at the sessions:

Dr. Mandred W. Comfort, Rochester, Minn., co-author, "Chronic Relapsing Pancreatitis."

Dr. Lester Dragstedt, Chicago, "The Role of Vagotomy in the Treatment of Peptic Ulcer."

Dr. Martin E. Rehfuss, Philadelphia, "Experimental Cholecystitis."

Drs. H. J. Moersch and B. R. Kirklin, Rochester, Minn., "Gastroscopy and Its Relationship to Roentgenology in the Diagnosis of Carcinoma of the Stomach."

Dr. Pedro L. Farinas Mayo, Havana, Cuba, co-author, "Postbulbar Duodenal Ulcers."

Dr. Martin G. Vorhaus, New York, "Hypertrophic Stenosis in the Adult."

Dr. Moses Paulson, Baltimore, co-author, "The Medical Management of Total Gastrectomy."

Drs. Henry A. Rafsky and Michael Weingarten (Associate), New York, "A Study of the Gastric Secretory Response in the Aged."

Dr. H. Marvin Pollard, Ann Arbor, "The Rate of Healing for Gastric and Duodenal Ulcers."

Dr. Lemuel G. McGee, Wilmington, Md., "Metabolic Disturbances in Workers Exposed to Dinitrotoluene."

Dr. J. A. Bargen, Rochester, Minn., co-author, "Amino Acid Alimentation in Gastrointestinal Diseases."

Drs. Burrill B. Crohn, New York, and Milford O. Rouse, Dallas, co-authors, "Trauma in Relationship to the Perforation of Peptic Ulcer."

Dr. A. F. R. Andresen, Brooklyn, N. Y., "Traumatic Perforation of the Rectum and Sigmoid."

Dr. Walter L. Palmer, Chicago, "Giant Hypertrophic Gastritis."

Dr. Henry J. Tumen, Philadelphia, co-author, "Backache Due to Intra-abdominal Disease."

The eleventh annual convention of the National Gastroenterological Association was held in New York, June 19–21. Dr. Anthony Bassler, F.A.C.P., president of the association, was chairman of the program committee, of which Dr. Samuel Weiss, F.A.C.P., also was a member. Dr. Bassler, Dr. Clarence J. Tidmarsh, F.A.C.P., Montreal, vice-president of the association, and Dr. Henry A. Rafsky, F.A.C.P., New York, presided at sessions. Papers were presented by the following members of the college:

Dr. Zacharias Bercovitz, F.A.C.P., New York, "Parasitology and Tropical Medicine from a Military and Civilian Standpoint";

Dr. M. Herbert Barker, F.A.C.P., Chicago, "Acute and Chronic Gastrointestinal Manifestation of Infectious Hepatitis";

Dr. Sidney A. Portis, F.A.C.P., New York (co-author), "Changes in the Function of the Stomach with Varying Emotional Scales";

Dr. Martin E. Rehfuss, F.A.C.P., Philadelphia, "The Evolution of Chronic Cholecystitis";

Dr. William B. Rawls, F.A.C.P., New York, "Socialized Medicine";

Dr. Henry A. Monat, F.A.C.P., "Gastroscopy."

Dr. Bassler, Dr. J. Russell Twiss, F.A.C.P., and Dr. Burrill B. Crohn, F.A.C.P., all of New York, were discussors of the scientific papers.

Dr. Lathan A. Crandall, F.A.C.P., formerly of the University of Tennessee, has accepted appointment as Director of the Research Laboratories, Miles Laboratories, Inc., Elkhart, Ind.

Dr. Julius H. Comroe, Jr., F.A.C.P., Philadelphia, formerly Assistant Professor of Pharmacology in the University of Pennsylvania School of Medicine, has been appointed Professor of Physiology and Pharmacology in the University's Graduate School of Medicine. Dr. Comroe succeeds Dr. Edward Lodholz, who has been appointed Emeritus Professor of physiology.

Dr. Ross Moore, F.A.C.P., Los Angeles, delivered three lectures on the subject of "Diagnosis without Tools," constituting the recent sixth annual series of Lecture Conferences of Hollywood Presbyterian Hospital.

Dr. Reginald Fitz, F.A.C.P., Boston, delivered an address at the unveiling in San Francisco, July 4, of the portrait of Dr. Oliver Wendell Holmes. This portrait, painted by the noted artist Dean Cornwell and entitled "That Mothers Might Live," is the sixth in a series of "Pioneers of American Medicine" commissioned by Wyeth Incorporated.

Dr. Robert U. Patterson, F.A.C.P., Baltimore, retired June 30 from the deanship of the University of Maryland School of Medicine. Dr. Patterson, a former Surgeon General of the U. S. Army, retired from the Army with the rank of Major General to become dean of the University of Oklahoma School of Medicine. He began his deanship at the University of Maryland in 1942.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, delivered an address on "The Psychobiology of Psychiatric Research" at the dedication of the new Research Laboratory of the McLean Hospital, Waverley, Mass. The Laboratory will concern itself with investigation of mental disease problems and with the training of graduate students in methods of research in psychiatry.

Dr. Francis F. Borzell, F.A.C.P., is the recipient for 1945 of the Dr. Isidor P. Strittmatter Award. The award, consisting of a gold medal and scroll, was made by the Philadelphia County Medical Society for Dr. Borzell's "outstanding services in behalf of the contributions of organized medicine to World War II and his sincere devotion and constructive effort in safeguarding the principles of the American system of medicine."

Dr. Kendall Elsom, F.A.C.P., Philadelphia, Pa., has been appointed consultant in gastro-enterology to the Veterans Administration for the hospitals of the Third District, including Pennsylvania, New Jersey, and Delaware.

Dr. Henry R. Carstens, F.A.C.P., 2nd Vice President of the College, 1942–1944, has been appointed Medical Director of Branch Office No. 3 of the Veterans Administration. This office has charge of veterans' affairs in the Third District, which consists of Pennsylvania, New Jersey and Delaware. His headquarters are at Philadelphia.

A veteran of both World Wars, Dr. Carstens served in the last war as Colonel in the U. S. Army, and commanded the 17th General Hospital, Naples, Italy. Before the war, Dr. Carstens held positions as Associate Professor of Clinical Medicine, Wayne University College of Medicine, Chief of the Division of Internal Medicine, Outpatient Department, Harper Hospital, and chief of the Department of Medicine, Florence Crittenton Hospital, Detroit, Mich.

Dr. Henry LeRoy Bockus, F.A.C.P., Philadelphia, Pa., has been awarded the honorary degree of Doctor of Science by Dickinson College.

Dr. Edward B. Krumbhaar, F.A.C.P., Professor of Pathology in the University of Pennsylvania School of Medicine, has recently been elected to membership in the Harvard Board of Overseers.

Dr. John T. Farrell, Jr., F.A.C.P., Philadelphia, Pa., spoke on "The Rôle of Roentgenology in the Diagnosis and Management of Pyloric Obstruction," before the Dauphin (Pa.) County Medical Society, June 4.

It was recently announced that Dr. Edward Weiss, F.A.C.P., Philadelphia, Pa., had been elected President of the American Society for Research in Psychosomatic Problems.

Dr. Lester Hollander, F.A.C.P., Pittsburgh, Pa., is the author of a report, published recently in the Pennsylvania Medical Journal, on "Deodorants—Facts and Fallacies."

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., recently addressed the Pennsylvania Dietetic Association on the subject, "Psychosomatic Medicine and Diet Therapy."

Dr. C. Howard Marcy, F.A.C.P., Pittsburgh, Pa., has retired from the presidency of the Pennsylvania Tuberculosis Society after a term of service of four years. Dr. John E. Fretz, F.A.C.P., Easton, Pa., has been elected first vice president of the Society; and Dr. T. Lyle Hazlett, F.A.C.P., Pittsburgh, Pa., and Dr. Elmer Highberger, F.A.C.P., Greensburg, Pa., have been elected to membership on its Board of Directors.

Colonel Allen Izard Josey, (MC), A.U.S., F.A.C.P., is the co-author of a recent paper in the Journal of the American Medical Association, entitled "Ruptured Intervertebral Disk Simulating Angina Pectoris."

Dr. David P. Barr, New York, President of the American College of Physicians, has been appointed a member of the newly organized Therapeutic Trials Committee of the American Medical Association. The purpose of this committee, which will function under the Council on Pharmacy and Chemistry, is to encourage sound evaluation of the clinical usefulness of new therapeutic agents. In this regard, the committee may assist pharmaceutical manufacturing firms in arranging clinical trials of new drugs. Other Fellows of the College who are members of the committee are

Dr. Chester S. Keefer, Boston; Dr. Walter W. Palmer, New York; Dr. W. Barry Wood, St. Louis; and Dr. Torald Sollmann, Cleveland.

A recent issue of the Journal of the American Medical Association contains an official statement by Dr. Cornelius P. Rhoads, F.A.C.P., New York, chairman of the Committee on Growth, National Research Council, on "Nitrogen Mustards in the Treatment of Neoplastic Disease."

Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, formerly Colonel in the Medical Corps, Army of the United States, has been awarded the Legion of Merit for outstanding service rendered by him while chief of medical service, Army Tropical Disease Center, Moore General Hospital, Swannanoa, N. C.

Dr. Thomas B. Magath, F.A.C.P., Rochester, Minn., formerly Commodore, Medical Corps, U. S. Naval Reserve, has been awarded the Legion of Merit for his studies and recommendations dealing with quarantine practices, concerning especially air traffic.

Dr. Albert M. Snell, F.A.C.P., Rochester, Minn., formerly Captain, Medical Corps, U. S. Naval Reserve, received commendation from the Secretary of the Navy for his "meritorious performance of duty as chief of the medical service, U. S. Naval Hospital, Oakland, Calif., March 20, 1944, to Nov. 5, 1945."

Dr. Samuel J. McClendon, F.A.C.P., San Diego, has become President of the California Medical Association. Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, has been designated as the Editor of the journal of the association, California and Western Medicine.

The board of trustees of the newly organized American Allergy Fund includes Dr. Harry L. Alexander, F.A.C.P., St. Louis; Dr. J. Harvey Black, F.A.C.P., Dallas; Dr. Milton B. Cohen, F.A.C.P., Cleveland; Dr. Francis M. Rackemann, F.A.C.P., Boston and Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Va. The purpose of this organization is to promote the study and public understanding of allergy.

Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C., has been appointed Adjunct Professor of Medicine in the Georgetown University School of Medicine.

Dr. John Favill, F.A.C.P., has been appointed head of neuropsychiatry at the Presbyterian Hospital, Chicago.

Dr. Abraham M. Balter, F.A.C.P., formerly of Aspinwall, Pa., has recently retired from military service in the Army with the rank of Lieutenant Colonel, after two and a half years' service, and is now on the staff of the Veterans Administration Hospital, Huntington, W. Va.

Dr. Nathaniel Uhr (Associate), formerly of New York City, has been retired from the Army with the rank of Colonel, after approximately four years' service, and has accepted an appointment at the Veterans Hospital, Topeka, Kan.

Dr. Olin B. Chamberlain, F.A.C.P., Charleston, S. C., has been elected president-elect of the South Carolina Medical Association.

At the annual meeting of the American College of Radiology, June 29, San Francisco, Dr. Edward H. Skinner, Kansas City, Mo., was elected president; Dr. Edwin C. Ernst, F.A.C.P., St. Louis, was elected vice-president.

Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army and Colonel Leon L. Gardner, F.A.C.P., Director of the Army Medical Library, have been granted honorary membership in the Brazilian Academy of Military Medicine.

Dr. Harold E. Himwich, F.A.C.P., Albany, New York, has accepted appointment as research physician, physician of clinical research branch of the Chemical Warfare Service, Edgewood Arsenal, Md. Dr. Himwich was formerly Professor of Physiology and Pharmacology in the Albany Medical College.

Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, served as chairman of the International Health Conference which took place in New York, N. Y., beginning June 20.

Dr. Maurice Fremont-Smith, F.A.C.P., Boston, was co-author of an article on "Cancer of Endometrium" recently published in the Journal of the American Medical Association.

Dr. Howard F. Root, F.A.C.P., Brookline, Mass., is a recent contributor to the Journal of the American Medical Association of a paper on "Allergy to Insulin."

It was announced recently that Major Gerald A. Beatty, F.A.C.P., Wilmington, Del., has been awarded the Bronze Star for his "energy, coöperative spirit, foresight and knowledge . . . exemplary devotion."

A portrait-medallion of Dr. Raymond B. Allen, F.A.C.P., has been presented to the President of the University of Illinois. Before his resignation from the University of Illinois to accept the presidency of the University of Washington, Dr. Allen had served as Executive Dean of the Chicago colleges and dean of the Medical School of the University of Illinois.

Drs. Morris M. Banowitch, F.A.C.P., and John B. D'Albora, F.A.C.P., Brooklyn, have received appointments as clinical professors in the department of medicine of the Long Island College of Medicine. Dr. Saverio C. Franco, F.A.C.P., has been appointed assistant clinical professor of medicine in the same medical school.

Dr. Joseph S. Hiatt, F.A.C.P., Sanitorium, N. C., has been appointed to the position of Superintendent of the Hugh Chatham Memorial Hospital in Elkin, N. C.

Dr. Edgar P. McNamee, F.A.C.P., Cleveland, has assumed the office of President of the Ohio State Medical Association.

Drs. Finley Gayle, Jr., F.A.C.P., Richmond, Va., and David C. Wilson, F.A.C.P., University, Va., participated in a neuropsychiatry seminar which was held at the Veterans Hospital, Roanoke, Va., in May.

At the recent annual meeting of the Association of American Physicians, Dr. O. H. Perry Pepper, formerly president of the American College of Physicians, was elected President of the Association. He succeeds as president Dr. Warfield T. Longcope, F.A.C.P. Also elected officers of the Association were Dr. Joseph T. Wearn, F.A.C.P., secretary, and Dr. Walter Bauer, F.A.C.P., Boston, treasurer.

Lt. Col. Joseph A. Resch, (MC), (Associate), has resigned his commission in the United States Army, effective September 14, 1946, and has received a fellowship in neurology at the University of Minnesota.

Dr. Anthony M. Kasich (Associate), Weehawken, N. J., addressed the American Association of the History of Medicine at Atlantic City, May 26, 1946, on the subject, "William Prout and the Discovery of Hydrochloric Acid in the Gastric Juices."

Col. Elias E. Cooley, F.A.C.P., has recently retired from the Medical Corps of the U. S. Army because of physical disability and is now residing at 12 Manly St., Greenville, S. C.

Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, has been appointed A.C.P. representative at the Fourth International Congress on Tropical Medicine and Malaria.

The 1947 Assembly of the Interstate Postgraduate Medical Association of North America, of which Dr. James E. Paullin, F.A.C.P., Atlanta, is president-elect, will be held in St. Louis, Mo., October 13–17, 1947.

A number of important appointments of members of the College to the faculty of the Medical College of Alabama, Birmingham, were among those recently announced by Dr. Roy R. Kracke, Dean. In the Department of Medicine, Dr. James S. McLester, F.A.C.P., has been made Professor and Chairman; Dr. Seale Harris, F.A.C.P., Professor emeritus; Dr. Edgar G. Givhan, Jr., F.A.C.P., Associate Professor; Dr. Joseph E. Hirsh, F.A.C.P., Associate Professor; Dr. James B. McLester, F.A.C.P., Associate Professor; Dr. James O. Finney, F.A.C.P., Assistant Professor; Dr. E. Dice Lineberry, F.A.C.P., and Governor for Alabama, Assistant Professor; Dr. R. Olney Russell, F.A.C.P., Assistant Professor; Dr. Ivan C. Berrey (Associate), Assistant Pro-

fessor. Dr. Tom D. Spies, F.A.C.P., has been appointed Visiting Professor of Research Medicine.

Dr. Claude C. McLean, F.A.C.P., received appointment in the Department of Pediatrics as Assistant Professor.

Dr. James J. Lightbody, F.A.C.P., Detroit, is Chairman of the Board of Trustees of the Wayne County Medical Society. Dr. Ralph A. Johnson (Associate), Detroit, is Editor of the Detroit Medical News.

The Twelfth Annual Meeting of the American College of Chest Physicians was held in San Francisco, June 27–30, 1946. Dr. J. Arthur Myers, F.A.C.P., Minneapolis, delivered the President's Address. Dr. James J. Waring, F.A.C.P., Denver, Colo., and Dr. Carl H. Gellenthien, F.A.C.P., Valmora, N. M., took part in a panel of medical experts.

A refresher course on Diseases of the Chest was a feature of the program. Among the participants in the course were Dr. R. H. Sundberg, F.A.C.P., San Diego, Calif., and Dr. Jacob J. Singer, F.A.C.P., Los Angeles, Calif.

Dr. Andrew L. Banyai, F.A.C.P., Milwaukee, Wis., served as co-chairman of the International Night Dinner program, at which Dr. William E. Ogden, F.A.C.P., Toronto, Ont., delivered a report. Dr. Banyai also presented a paper at the scientific sessions on "Inhalation of Carbon Dioxide for the Management of Cough." Dr. Frank N. Allan, F.A.C.P., Boston, Mass., was co-author of a paper on "Thymectomy in the Treatment of Myasthenia Gravis," and Dr. Alfred Goldman, F.A.C.P., San Francisco, Calif., reported on "The Surgical Treatment of Bronchial Adenoma."

Dr. H. Sheridan Baketel, F.A.C.P., of Greenland, N. H., received a certificate from the New Hampshire Medical Society at its 177th meeting last May in recognition of 50 years of continuous membership in that Society.

United States Public Health Service Makes Grant for Cancer Research

A total of approximately $50,000 in grants in aid to several American universities for cancer research has been approved by the U. S. Public Health Service Federal Grant Agency upon the recommendation of the National Advisory Cancer Council.

The University of Virginia will receive $15,000 for a study of the fractionation of proteins of normal and cancerous tissues and of reactions to chemotherapeutic agents, and $3,550 for work on the synthesis of compounds causing cancer cell damage.

George Washington University, Washington, D. C., received one grant of $2,100 for a study of the effect of vitamin E on the growth and incidence of spontaneous and induced tumors in mice, and $2,500 for a program of study of the toxicity, metabolism, physiological and pharmacological actions of substances that may be useful in destroying cancerous tissue or in halting its growth.

The University of Rochester, Rochester, N. Y., received $10,000 for studies of gastric secretions in patients with cancer of the stomach.

Johns Hopkins University, Baltimore, Md., received $7,700 for the study and control of enzymatic activity in relation to agents that interfere with the metabolism of normal and cancerous cells.

Loyola University, Chicago, Ill., received $2,847 to support a study of the pathogenesis of experimental brain tumors.

Northwestern University, Chicago, Ill., received $2,500 for the study of synthesis of hydrocarbons structurally related to the steroids.

The University of Minnesota, Minneapolis, Minn., received $2,100 to support a study of gastritis in relation to carcinoma of the stomach.

Carson-Newman College, Jefferson City, Tenn., received $700 to support work on the preparation of compounds for testing in the chemotherapy program on cancer.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to July 12, 1946 inclusive).

Theodore J. Abernathy, Washington, D. C. (Major, MC, AUS)
Glen I. Allen, Peoria, Ill. (Lt. Col., MC, AUS)
John S. Atwater, Rochester, Minn. (Lt., MC, USNR)

Abraham M. Balter, Aspinwall, Pa. (Lt. Col., MC, AUS)
Wayne C. Barnes, Springfield, Mass. (Major, MC, AUS)
Nathan J. Bender, Shreveport, La. (Lt., MC, USNR)
James L. Borland, Jacksonville, Fla. (Major, MC, AUS)
Lewis H. Bronstein, New York, N. Y. (Major, MC, AUS)
Frederic J. Burns, Pawtucket, R. I. (Lt. Comdr., MC, USNR)
M. Paul Byerly, Baltimore, Md. (Capt., MC, AUS)

Russell J. Callander, Tucson, Ariz. (Lt. Comdr., MC, USNR)
Julius Chasnoff, New York, N. Y. (Lt. Col., MC, AUS)
Samuel Cohen, Jersey City, N. J. (Capt., MC, AUS)
Frederick S. Coombs, Jr., Youngstown, Ohio (Lt. Col., MC, AUS)

Robert K. Dixon, Denver, Colo. (Lt. Col., MC, AUS)
Charles H. Drenckhahn, Champaign, Ill. (Lt. Col., MC, AUS)

Henry D. Ecker, New Orleans, La. (Surgeon, USPHS)

Henry Felson, Cincinnati, Ohio (Lt. Col., MC, AUS)

John F. Giering, Wilkes-Barre, Pa. (Lt. Col., MC, AUS)
William H. Gordon, San Francisco, Calif. (P. A. Surgeon, USPHS)

Meyer M. Harrison, Louisville, Ky. (Capt., MC, AUS)

R. Harold Jones, Fairmont, W. Va. (Col., MC, AUS)
Frank T. Joyce, Chickasha, Okla. (Capt., MC, AUS)

Newton A. Kilgore, Jr., Houston, Tex. (Lt. Col., MC, AUS)
Laurance W. Kinsell, East Stroudsburg, Pa. (Lt., MC, USNR)
Richard S. Knowlton, Cleveland, Ohio (Major, MC, AUS)
Alvin B. C. Knudson, Dwight, Ill. (Major, MC, AUS)

Herbert P. Lenton, Carlisle, Pa. (Capt., MC, AUS)
J. Elliot Levi, Baltimore, Md. (Capt., MC, AUS)

Robert M. Lintz, New York, N. Y. (Comdr., MC, USNR)
Stephen L. Lirot, Meriden, Conn. (Lt., MC, USNR)
Joseph Litwins, New York, N. Y. (Lt. Col., MC, AUS)

Harold F. Machlan, Hines, Ill. (Col., MC, AUS)
L. Martin Mares, Wenatchee, Wash. (Lt. Col., MC, AUS)
Shaw McDaniel, Houston, Tex. (Comdr., MC, USNR)
Milton Mendlowitz, New York, N. Y. (Major, MC, AUS)
William C. Menninger, Topeka, Kan. (Brig. Gen., MC, AUS)
William R. Minnich, Atlanta, Ga. (Capt., MC, AUS)
Thomas C. Monaco, Boston, Mass. (Capt., MC, AUS)
Raymond W. Monto, Detroit, Mich. (Major, MC, AUS)
Sylvan E. Moolten, New York, N. Y. (Lt. Col., MC, AUS)
Franklin D. Murphy, Philadelphia, Pa. (Capt., MC, AUS)

Benjamin H. Neiman, Chicago, Ill. (Lt. Col., MC, AUS)
James K. Norman, New Orleans, La. (Surgeon, USPHS (R))

Howard M. Odel, Rochester, Minn. (Lt. Comdr., MC, USNR)

J. Winthrop Pennock, Syracuse, N. Y. (Lt. Col., MC, AUS)

William S. Randall, Jr., Pensacola, Fla. (Major, MC, AUS)
Robert A. Reading, Cleveland, Ohio (Comdr., MC, USNR)

Emmett L. Schield, Pomona, Calif. (Lt. Col., MC, AUS)
Leo V. Schneider, Glenn Dale, Md. (Lt. Col., MC, AUS)
Maurice A. Schnitker, Toledo, Ohio (Lt. Col., MC, AUS)
John W. Shuman, Sr., Santa Monica, Calif. (Col., MC, AUS)
Wilbur A. Smith, New York, N. Y. (Lt. Col., MC, AUS)

Robert H. Talkov, Brookline, Mass. (Capt., MC, AUS)

Nathaniel Uhr, New York, N. Y. (Lt. Col., MC, AUS)
William G. Ure, Tucson, Ariz. (Capt., MC, AUS)

Wesley Van Camp, Detroit, Mich. (Surgeon, USPHS (R))

Robert C. West, Hamilton, Tex. (Lt. Col., MC, AUS)
Paul L. White, Austin, Tex. (Lt. Col., MC, AUS)

It is intended to publish in book form a collection of subjective case histories written by physicians.

Such reports should cover a much broader field than that which is customarily called symptoms. The term "symptoms" is used to mean the total subjective experience of the patient caused by disease. To the commonly acknowledged symptoms, such as pain, fatigue, nausea, etc., must be added such subjective experiences as are related to the mental, emotional and economic aspects. Any subjective experience proceeds not in a theoretical vacuum of the "normal" or "average" person, but within the canvass of an established personality with all the modalities of intellect, emotions,

faith, codes of behavior, social and economic realities. The argument may then well be encompassed in two main questions:

1. How has my personality (in the fullest sense of the word) modified the disease? and
2. How has the disease modified my personality?

The writer believes that much more specifically directed work is urgently needed. He believes that one particularly fertile approach to this problem is to induce physicians to analyze and describe their own experiences with diseases they have or have had.

It would seem that the combination of objective medical knowledge with the subjective experience might be particularly fruitful of original contributions in this field.

In such a collection, emphasis should be placed on chronic or recurrent diseases, because they are likely to show, more than the acute ones, modifications caused by the patient's individuality, and more of such significant marks that diseases may leave on the individual in his mental, emotional, physical, social and professional life.

Each contributor should be limited by no other concern but the general aim of the collection. It is, therefore, expected that objective clinical details be limited to that minimum that is germane to the story. Full emphasis should be given to subjective symptoms, especially to those that the usual textbooks consider unessential or fail to mention. Considerable details are expected in the matter of psychological attitude to the disease as such, to pain, to the prognosis—right or wrong—to the limitations imposed by the disease or its consequences, to accomplished or attempted readjustments, and to peculiarities of the premorbid personality if it is essential to the total picture.

In many discussions that the writer has had while this plan slowly matured, the main and first objection raised was the impossibility of getting "unbiased accounts." This is simply met by the answer that unbiased accounts are neither expected nor desired, since it is precisely the individual experience that should be told.

Each contributor will have the choice whether or not he wishes to remain anonymous; and, if anonymity is desired, it will be strictly maintained.

Physicians, who may be interested to contribute reports of their illnesses, are invited to write to

MAX PINNER, M.D., *Editor*
AMERICAN REVIEW OF TUBERCULOSIS
463 Vermont Avenue
Berkeley 7, California

SPECIAL NOTICE

The Department of Medicine of the New York Post-Graduate Medical School and Hospital has available, for September 1, 1946, a Research Assistantship in Medicine. This project is a detailed clinical investigation of the ageing process in its various phases. Stipend to begin at $2400 yearly in proportion to qualifications of candidate.

Requirements include graduation from a Grade A medical school in this country and several years training in an approved hospital, preferably a residency in medicine.

Inquiries and applications should be addressed to the Department of Medicine, New York Post-Graduate Medical School and Hospital, 301 East 20th Street, New York 3, New York.

Reading Lists and Bibliographies

By direction of the Board of Regents the Advisory Committee on Postgraduate Courses of the College attempts to obtain reading lists for each postgraduate course for publication in this journal, making these lists available to the entire membership of the College, in addition to better preparing the men who will take the courses. These lists are not to be considered all inclusive.

Allergy

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The Specificity of Serological Reactions. Karl Landsteiner. Harvard University Press, Cambridge, Mass., 1945.

Hay Fever Plants. R. P. Wodehouse. Chronica Botanic Co., Waltham, Mass., 1945.

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Anaphylaxis. Hypersensitiveness and Allergy. W. W. C. Topley. An Outline of Immunity, Chapter 12, p. 192. Wm. Wood Co., 1935.

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Herter Lectures. H. H. Dale. Bulletin Johns Hopkins Hospital 31: pp. 257, 310, 373, 1920.

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The Placental Transmission of Antibodies in the Skin-Sensitive Type of Human Allergy. W. B. Sherman, S. F. Hampton and R. A. Cooke. J. Exper. Med. 72: 611, 1940.

The Question of the Elimination of Foreign Protein (Eggwhite) in Woman's Milk. H. H. Donnally. J. Immunol. 19: 15, 1930.

The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin. E. L. Burky. J. Allergy 5: 466, 1934.

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The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma: Analysis of the Causative Factors. F. F. Furstenberg and L. N. Gay. Bull. Johns Hopkins Hospital 60: 412, 1937.

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Studies in Specific Hypersensitiveness. IV. New Etiologic Factors in Bronchial Asthma. R. A. Cooke. J. Immunol. 7: 147, 1922.

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Seasonal Hay Fever and Asthma Due to Molds. S. M. Feinberg. J. A. M. A. 107: 1861, 1936.

Importance of Allergy in Etiology and Treatment of Nasal Mucous Polyps. R. A. Kern. J. A. M. A. 103: 1293, 1934.

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Evaluation of the Ragweed Hay Fever Resort Areas of North America. O. C. Durham. J. Allergy 8: 175, 1937.

Moisture Characteristics of Pollen. A. B. Berresford and Robert A. Cooke. J. Allergy 16: 87, 1945.

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Treatment of Asthma and Hay Fever. Robert A. Cooke. New York State J. Med. 43: 17, 1943.

Allergy of the Digestive System

Allergy of the Abdominal Organs. M. Walzer. J. Lab. & Clin. Med. 26: 1867, 1941.

Gastro-intestinal Manifestations of Allergy. R. A. Cooke. Bull. N. Y. Acad. Med. Second Series IX: 15, 1933.

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The Treatment of Infantile Eczema from the Point of View of the Pediatrician. L. W. Hill. J. A. M. A. 111: 2113, 1938.

A Consideration of Some Allergy Problems. I. Allergic Dermatitis (Eczema). Robert A. Cooke. J. Allergy 15: 203, 1944.

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Transient Focal Pulmonary Edema. C. B. Peirce, E. F. Crutchlow, A. T. Henderson and J. W. McKay. Am. Rev. Tuberc. 52: 1, 1945.

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Principles and Practices of Inhalational Therapy. Alvan L. Barach. J. B. Lippincott Co., Philadelphia, 1944.
Cerebral Symptoms Induced by Angioneurotic Edema. F. Kennedy. Arch. Neurol. and Psychiat. 15: 28, 1926.
Allergic Migraine. W. T. Vaughan. J. A. M. A. 88: 1983, 1927.
Food Allergy in Henoch's Purpura. H. L. Alexander and C. H. Eyermann. Arch. Dermat. & Syph. 16: 332, 1927.
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Allergy in Drug Idiosyncrasy. R. A. Cooke. J. A. M. A. 73: 759, 1919.

OBITUARIES

DR. EMANUEL LIBMAN

Dr. Emanuel Libman died in Mt. Sinai Hospital on June 28, 1946, at the age of seventy-three. Dr. Libman was born August 22, 1872, in New York City; attended the College of the City of New York and received his medical degree from Columbia University College of Physicians and Surgeons, 1894. For many years Professor of Clinical Medicine at his Alma Mater; consulting physician, Mt. Sinai, Montefiore, Harlem, Beth Israel, French, Methodist (Brooklyn), Bronx, Israel-Zion (Brooklyn), and Beth-El (Brooklyn) Hospitals, and Hospital for Deformities; author of numerous publications; former President, New York Pathological Society; Member, New York Academy of Medicine, American Society of Clinical Investigation, Harvey Society, American Association of Immunologists, Association of American Physicians, and many others; Diplomate, American Board of Internal Medicine; Fellow, American College of Physicians since 1928.

Dr. Libman was a very famous internist, a stimulating teacher and possessed a keen mind for research, and his loss to the medical profession will be very keenly felt.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. MORTIMER COHEN

Dr. Mortimer Cohen, F.A.C.P., of Pittsburgh, Pennsylvania, died suddenly on June 20, 1946, at the age of 49 years. Dr. Cohen received his public school and high school education in the schools of the City of Pittsburgh. He received both his college and medical school education at the University of Pittsburgh, graduating from the School of Medicine in 1921. He served his internship at Passavant Hospital, Pittsburgh, after which he became associated with The Elizabeth Steel Magee Hospital and the Department of Pathology, University of Pittsburgh. This association was on a full time basis, beginning the latter part of 1922 and continuing until the time of his death. His work in connection with the Hospital and the School was confined to the field of Pathology. He became Associate Professor of Pathology in 1928. As a teacher of Pathology and as a Pathologist to the Hospital, his work was of the highest quality. As a consultant in Pathology his judgment and advice will be greatly missed by his associates. He was a Diplomate of the American Board of Pathology, a Fellow of the American College of Physicians (1932), a Fellow of the American Medical Association, and a member of The Pennsylvania Medical Society, Allegheny County Medical Society, The Association of Pathologists and Bacteriologists, The American Society of Clinical Pathologists, International Association of Medical Museums, The Clinical Pathological Society of Pittsburgh, Society of Biological Research, Sigma Xi and Alpha Omega Alpha.

Dr. Cohen's untiring devotion to his work was always an inspiration to his associates; especially was this true during the trying years of World War II.

On the evening of June 20 while working in his laboratory at the Hospital he suffered an attack of coronary thrombosis from which he died a few hours later.

His passing is a distinct loss to the medical profession.

GEORGE R. LACY, M.D., F.A.C.P.

COLONEL WALTER STEEN JENSEN

Colonel Walter Steen Jensen, M.C., died in Washington, D. C., on April 3, 1946.

An outstanding medical officer who was exceptionally well-liked by his fellow officers, he was commissioned October 29, 1925. At the time of his death Colonel Jensen was on duty in the Office of The Air Inspector, Headquarters, Army Air Forces. His death came as a shock to his many close friends who knew and loved him.

Born the son of Danish immigrant parents on August 11, 1894, in Brooklyn, N. Y., the late Colonel Jensen served overseas as an enlisted man in World War I. While in action with the 151st Field Artillery, 42nd Division (Rainbow Division), he was awarded the Purple Heart and an Oak Leaf Cluster for meritorious service, in addition to many campaign ribbons.

Early in World War II, Colonel Jensen was a member of the pioneer American mission which flew from Alaska to Moscow. In 51 days during which he studied Russian technics of aviation medicine, Colonel Jensen's observations resulted in important medical information to the United States Army. He was awarded the Legion of Merit for his work in connection with that mission. For security reasons, the medal was not awarded him until 1945.

From then on Colonel Jensen specialized in aviation medicine and was named Deputy Air Surgeon the same year. Later he served as Air Surgeon for the Pacific Theater before moving up into battle zones on the staff of Lieutenant General Barney Giles.

Upon his return from the Pacific early this year, the deceased Army officer was assigned temporarily to the Office of the Air Surgeon.

An accomplished administrator, Colonel Jensen served as executive officer in the Army and Navy General Hospital, Hot Springs, Ark., commencing in 1937. When war broke out he was Medical Director, Newfoundland Base Command, and served as liaison officer between the U. S. Army and Newfoundland health authorities.

An aviation enthusiast, Colonel Jensen attended the School of Aviation Medicine, Randolph Field, Texas, where he taught on the faculty and also served as Director of Neuropsychiatry at the school. Prior to that he was Chief, Neuropsychiatric Section, Gorgas Hospital, Panama. He also took

postgraduate work at Army Medical Center, Walter Reed General Hospital, Washington, as far back as 1928.

Upon his discharge from the Army following World War I, Colonel Jensen completed his college studies and graduated from Union College, Lincoln, Neb., with an A.B. degree in 1920. Four years later he received his M.D. degree from College of Medical Evangelists, Los Angeles, Calif. He completed his internship at White Memorial Hospital, California. He was commissioned a First Lieutenant, Medical Corps, on October 29, 1925.

The deceased was a Fellow in The American College of Physicans. He held membership in American Medical Association, American Psychiatric Association, and Association of Military Surgeons of the United States. He was author of several published articles and "Outline of Neuropsychiatry."

Major General NORMAN T. KIRK, M.D., F.A.C.P.,
Governor for the Medical Corps, U. S. ARMY.

DR. FRANCIS L. BARTHELME

Dr. Francis Lorraine Barthelme, B.S., M.D. (Associate), Effingham, Ill., died in St. Anthony's Hospital on March 8, 1946. He was 49 years old. Dr. Barthelme was graduated from the St. Louis University School of Medicine in 1923. He was attending Physician at St. Anthony's Hospital for a number of years and was formerly a member of the staff of the Evangelical Deaconess Hospital of St. Louis; elected an Associate of the College in 1928, before limitation was placed on the maximum Associate term; entered the medical corps of the Army of the United States on September 22, 1942 as Captain; service was terminated in November, 1943.

Dr. Barthelme is survived by his wife and three children.

DR. ALBERT SOILAND

Albert Soiland, M.D., D.M.R.E., F.A.C.P., internationally known radiologist of Los Angeles, California, died of a heart attack on May 14, 1946, while visiting at Stavanger, Norway.

Dr. Soiland was born at Stavanger on May 5, 1873. When a small boy he came to the United States. Later he attended the University of Illinois and in 1900 received his M.D. degree from the University of Southern California School of Medicine. He later became professor of radiology at this institution.

Dr. Soiland became interested in roentgenology and the treatment of cancer before he had graduated in medicine. He established the first x-ray office in Southern California. He founded, and was the Past President of the American College of Radiology; Past President, Radiological Society of North America; Past President, American Radium Society; Founder and Past Chairman, Section of Radiology, American Medical Association; Member, American Society for the Control of Cancer; Fellow (Honorary), Northern Society for Medical Radiology (Scandinavia); Member, Board of

Trustees, Pan American Medical Association; Member of the American Roentgenology Society; Diplomate of American Board of Radiology. He had been a Fellow of the American College of Physicians since 1917. Dr. Soiland was the author of numerous publications, and had studied in most of the important cancer clinics throughout the world.

He was prominently associated with yachting on the Pacific Coast and had organized, and was the first commodore of the Newport Harbor Yacht Club in 1914. He also was commodore of the Pacific Coast Yacht Association, and was instrumental in establishing the Trans-Pacific Yacht races of Hawaii, taking part in three of these and winning one.

He served in World Wars I and II and rose to the rank of Captain in the U.S. Naval Reserve and was said to be the oldest Captain on active duty.

Some time before his death, he created the Albert Soiland Cancer Foundation. This is a non-profit corporation which will ultimately control all of the property owned by Dr. Soiland and his widow, Mrs. Dagfine B. Soiland. This research foundation will endow fellowships in cancer research.

Dr. Soiland was a Mason and a member of many local clubs and organizations. Phi Rho Sigma and Theta Nu Epsilon were his fraternities.

The American College of Physicians has lost one of its most distinguished members.

LELAND HAWKINS, M.D., F.A.C.P.
Governor for Southern California

DR. I. HARRIS LEVY

Dr. I. Harris Levy, F.A.C.P., age 77 years, died in his sleep on July 9, 1946.

Dr. Levy was one of the first physicians in Syracuse to use the stomach tube in diagnosis. He also was one of the first to use roentgen-ray studies of the gastrointestinal tract. He was considered an authority on gastrointestinal disease and was highly respected in Central, Northern and Southern New York State. He had a large private and consulting practice.

Dr. Levy was an ardent student and a very keen clinician. For many years he was attending physician at the University Hospital. During his service he had the privilege of seeing many cases of typhoid fever and it was the privilege of the writer to work with him at that time. Dr. Levy's service at that time was the first to use the Coleman-Shattuck diet for the treatment of typhoid fever.

Dr. Levy traveled extensively and studied many times in Europe at the clinics in Berlin and Vienna. His hobbies were golf and archeology.

He was a diplomate of the American Board of Internal Medicine; a member of the American Gastro-Enterological Society, the New York State Medical Society, the Syracuse Academy of Medicine and the Practitioners' Club. He was also a member of Phi Beta Kappa and Alpha Omega Alpha,

honorary scholastic societies. He had been a Fellow of the American College of Physicians since 1916, almost from the inception of the College. He taught in the Syracuse University College of Medicine for over fifty years. He retired from the professorship of Medicine in 1931, since which time, until the time of his death, he was professor emeritus.

Dr. Levy was very highly respected for his learning and his scholastic attainments. He was a very skillful physician. He had many friends throughout the country. His death will be mourned by many and his loss to the medical profession will be keenly felt.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

CAPTAIN EARL CURTIS CARR

Captain Earl Curtis Carr, (MC), USN, died on May 9, 1946, at the Naval Hospital, Philadelphia, Pennsylvania. Until a short time before his admission to the Naval Hospital, Philadelphia, he had been Medical Officer in Command of the Naval Hospital, Norman, Oklahoma. Captain Carr was born June 13, 1892, at Fulton, Illinois. He graduated from the Medical School, University of Illinois, with the degree Doctor of Medicine in 1915, and served an internship at St. Louis City Hospital, 1915–1916, and as resident physician in the Louisville City Hospital. He entered the Naval Medical Reserve Corps in 1916. He was commissioned in the Medical Corps, U. S. Navy, June 5, 1917.

His service in the Navy included duty at the Naval Air Station, Pensacola, Navy Yards at New York and Philadelphia, Naval Training Station, Great Lakes, Illinois, and the Bureau of Medicine and Surgery. During World War I he served on the USS ST. LOUIS from June 1917 to October 1919. He completed a postgraduate course at the Naval Medical School and a postgraduate course in internal medicine. He was a Fellow of the American College of Physicians, the American College of Chest Physicians, and the Association of Military Surgeons of the United States. Captain Carr is survived by his wife and a son, William. Mrs. Carr is a sister of Commander W. B. Hetfield, (MC), USN, (Ret.). Captain Carr also had a brother in the Medical Corps of the Navy, Captain Claude W. Carr.

Funeral services and burial were on May 13 in Arlington National Cemetery.

ROSS T. MCINTIRE, Vice Admiral, Medical Corps,
Surgeon General, U. S. Navy,
Governor, American College of Physicians